2015-1654

United States Court of Appeals for the Federal Circuit

IN RE: OXYCONTIN ANTITRUST LITIGATION

PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., PURDUE PHARMACEUTICALS L.P.,

Plaintiffs-Appellants,

v.

AMNEAL PHARMACEUTICALS, LLC,

Defendant-Appellee.

Appeal from the United States District Court for the Southern District of New York in No. 1:13-cv-03372-SHS, Judge Sidney H. Stein.

BRIEF OF PLAINTIFFS-APPELLANTS PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., AND PURDUE PHARMACEUTICALS L.P.

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CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, counsel for Plaintiffs-Appellants certifies as follows:

1. The full name of every party represented by me in this case is:

   Purdue Pharma L.P., The P.F. Laboratories, Inc., Purdue Pharmaceuticals L.P.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

   N/A

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

   None

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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TABLE OF ABBREVIATIONS

The following abbreviations are used in this brief. Emphasis throughout the brief is added unless otherwise noted.

Abbreviation	Term
'591 application	WO 99/44591
'888 patent	U.S. Patent No. 8,337,888
'963 patent or McGinity	U.S. Patent No. 6,488,963
A__	Appendix page
Amneal	Amneal Pharmceuticals, LLC
ANDA	Abbreviated New Drug Application
API	active pharmaceutical ingredient
Bastin	WO 95/20947
cP	centipoise
CPDD	Committee/College on Problems of Drug Dependence
Defendants	Amneal Pharmaceuticals, LLC and Teva Pharmaceuticals USA, Inc.
Endo	Endo Pharmaceuticals, Inc.
FDA	U.S. Food and Drug Administration
Hoffmeister	U.S. Patent No. 4,070,494
Joshi	U.S. Patent Application No. US 2002/0187192; Provisional Application No. 60/287,509
McGinity and Zhang application	WO 97/49384
mL or ml	milliliter
NDA	New Drug Application
OROS	osmotic [controlled] release oral [delivery] system
PEO	polyethylene oxide
Plaintiffs	Purdue Pharma L.P.; The P.F. Laboratories, Inc.; and Purdue Pharmaceuticals L.P.
PTO	U.S. Patent and Trademark Office

TABLE OF ABBREVIATIONS
(continued)

Purdue	Purdue Pharma L.P.; The P.F. Laboratories, Inc.; and Purdue Pharmaceuticals L.P.
Royce	U.S. Patent No. 5,273,758
Schramm	Gebhard Schramm, A Practical Approach to Rheology and Rheometry (2d ed. 2004)
Shaw	U.S. Patent No. 3,980,766
Teva	Teva Pharmaceuticals USA, Inc.
Zhang dissertation	Zhang, Hot-Melt Extrusion as a Novel Technology to Prepare Sustained-Release Dosage Forms (Dec. 1999) (unpublished Ph.D dissertation, University of Texas at Austin)

STATEMENT OF RELATED CASES

The following consolidated appeals currently pending before the Court relate to the same New Drug Application at issue in this case: *Purdue Pharma L.P. v. Teva Pharmaceuticals USA, Inc.*, Nos. 2014-1311, -1312, -1313, and -1314; *Purdue Pharma L.P. v. Epic Pharma, LLC*, No. 2014-1294; *Purdue Pharma L.P. v. Mylan Pharmaceuticals Inc.*, No. 2014-1296; and *Purdue Pharma L.P. v. Amneal Pharmaceuticals, LLC*, Nos. 2014-1306 and -1307. As part of the trial record in this case, the parties in this appeal adopted the trial record from the consolidated appeals noted above.

STATEMENT OF JURISDICTION

The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). The court entered final judgment on April 9, 2015. (A94.) Purdue timely filed a notice of appeal from this final judgment on May 8, 2015. (A2800.) This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

The '888 patent-in-suit is directed to an abuse-deterrent, controlled-release oxycodone formulation having a PEO-containing gelling agent that, when tampered with and exposed to moisture, causes the formulation to become a viscous gel that impedes abuse by injection or snorting—without disrupting its controlled-release, 12-hour therapeutic effect. The resultant gel makes those methods of abuse difficult and unattractive to abusers. The questions presented are:

1. Did the district court err by finding the '888 patent's inventive solution to oxycodone abuse obvious, where: (a) the prior art taught away from combining gelling agents with an active ingredient in a controlled-release formulation, because gelling agents were understood to interfere with the intended release of the active ingredient for legitimate users; (b) the prior art failed to disclose all of the claim limitations, in particular the specific claimed viscosity levels; and (c) the objective, real-world evidence, including FDA's initial skepticism and later recognition of the features of Purdue's Reformulated OxyContin® embodying the '888 inventions, demonstrates nonobviousness?

2. Did the district court err by finding that the '888 patent's lack of explicit disclosure of a precise shear-rate range for viscosity testing rendered claim 7 indefinite, even though: (a) one of ordinary skill would know to assess viscosity in the zero-shear range to approximate the manipulated material's static state, *i.e.*,

as abusers would use it; and (b) even the shear-rate range utilized by the court nonetheless provided reasonable certainty as to the scope of the claim—such that the court itself had no difficulty finding infringement of claim 7?

STATEMENT OF THE CASE

A. Preliminary Statement

OxyContin® is a powerful pain medicine designed to deliver its large dose of oxycodone active ingredient slowly over time—known as "controlled release"—to provide patients in severe pain with 12 hours of relief per dose. OxyContin®'s original formulation, however, was widely abused. Seeking an instant and powerful "high," abusers would crush the 12-hour tablet, thereby reducing it to an immediate-release fine powder, and then either snort the powder or inject it after adding water and drawing it into a syringe. The consequences of that abuse—including addiction, overdose, and death—were devastating.

In addition to taking other measures to assist in addressing this terrible public-health problem, Purdue created a new product—Reformulated OxyContin®—that uses several patented technologies, including: (1) tablet hardness, to resist efforts to crush the tablets into powder in the first place, and (2) gelling, to impede snorting and injecting of any powder or fine particles that might result from abusers' extraordinary crushing efforts, but without either type of technology disrupting the controlled-release profile and 12-hour therapeutic

effect of the medicine. FDA approved this new product in April 2010. In the ensuing years, data indicated that Reformulated OxyContin® successfully reduced intranasal and intravenous abuse of the medicine. In light of the data, in April 2013, FDA not only granted Reformulated OxyContin® the first-ever opioid abuse-deterrent labeling, but also refused, for public-safety reasons, to approve any generic versions of OxyContin® lacking these abuse-deterrent qualities. The '888 patent covers certain anti-abuse gelling properties incorporated into Reformulated OxyContin®.

B. The Abuse Of Oxycodone

Oxycodone belongs to the opioid (or opiate) class of drugs that has been abused for centuries. (A2880-82.) As early as the 1920s, the National Academy of Sciences established and tasked the CPDD to find ways to reduce opioid abuse through regulation. (A2880-82.)

Opioid abuse continued to escalate, particularly in the 1990s, and by the early 2000s, opioid abuse had surged to create a national health crisis. (A2882-85.) To address the problem, scientists studied how abusers manipulate opioids in order to devise methods to deter that abuse while still providing safe treatment for patients using opioids properly. (A5331; A5416-17; A5422-24.) They learned that abusers generally prefer to use insulin syringes; in addition to being widely available, insulin syringes were less likely to catch the suspicion of authorities and

also used fine-gauge needles that were less painful and less likely to cause scarring. (A2909-10; A5304-05; A5421-22; A5447-48; A5595; A62290-92.)

Purdue's OxyContin®, which is used to treat severe pain requiring around-the-clock treatment, became a target of abuse. Initially approved in 1995, OxyContin® was a groundbreaking treatment for patients suffering chronic pain. But many of the features that made it so effective for such patients—including its "strength, duration, and known dosage"—also made it attractive to abusers. (A44724-29; A2883-84.)

C. Purdue Develops A New, Abuse-Deterrent Formulation That Includes A Gelling Agent To Impart Particular Viscosities

In the early 2000s, Purdue, along with government authorities and regulators, and other researchers, recognized the urgent need to address the oxycodone abuse epidemic. Purdue tried to deter abuse of OxyContin® through various means. It presented education programs to physicians and patients, and in consultation with FDA, included enhanced safety warnings on its labeling. (A44730-31.) Purdue even withdrew its highest dosage strength from the market. (A2884; A29585.) Despite these efforts, OxyContin® abuse continued. (A44311-12.)

Purdue and others also sought to develop new formulations that would deter abuse but still deliver the therapeutic API to the patient in a controlled-release manner. (A44728.) Purdue had been researching abuse deterrence for opioids as early as 1997, focusing on hydrocodone at the FDA's behest. (A2936-40.) When

abuse of OxyContin® dramatically increased at the turn of the twenty-first century, scientists at Purdue shifted their focus to deterring abuse of that drug. (A2884-85; A2940; A5300-01.)

As a 2003 CPDD paper later explained, researchers at the time generally employed "[t]wo main strategies." (A45057-74 at A45066.) One approach was to include in the formulation an antagonist, another drug substance that would block the opioid's effects when the formulation was abused. (A2889-91; A45066-67.) The other approach was to use a controlled-release profile to deliver the medication (which OxyContin® was already doing). Controlled-release properties (sometimes called "extended-release" or "sustained-release" properties) were thought to reduce the abuse potential of the drug because they would delay absorption of the opioid "compared with rapid onset or immediate release formulations," making the drug less likely to produce a "rush" that abusers seek. (A45066.) In fact, widespread abuse of controlled-release OxyContin® was unanticipated—FDA originally believed that OxyContin® would have *reduced* abuse potential because of its controlled-release formulation. *See generally* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm (last visited August 11, 2015).

Abusers, however, quickly found they could abuse OxyContin® and defeat its controlled-release mechanism by crushing the tablet into powder and then, most

dangerously, either snorting or, after mixing it with water, injecting the drug. (A59; A2873-80; A2883-84; A2941-42; A5301; A44726.) By doing so, abusers could access essentially 12 hours' worth of oxycodone in a matter of seconds, thereby obtaining a powerful and dangerous "high." (A126 ("Drug abusers typically may take a controlled-release product and crush, shear, grind, chew, dissolve and/or heat, extract or otherwise damage the product so that the full contents of the dosage form become available for immediate absorption by injection, inhalation, and/or oral consumption."); A58-59; A44725; A45066; *see also, e.g.*, A61516 (patented "Controlled Release Oxycodone Compositions" covering OxyContin®).)

When Purdue began its abuse-deterrent OxyContin® development project in 2001, the challenge was to deter abuse but still preserve the drug's efficacy for legitimate users. (A2945-46; *accord* A3185; A5361; A5366; A5396-97 (similar concerns of Grünenthal, another company working to develop abuse-deterrent opioids, for its different gelling technology).) The attempted approaches therefore needed to avoid any disruption of the drug's release profile. Purdue scientists tried combining oxycodone with antagonists, which seemed promising for abuse deterrence, but they grew concerned that antagonists could leak or otherwise block pain relief for legitimate users. (A2940-46; A5302-04.) They also tried bittering agents and dyes that would make illicit use undesirable. (A5303-04.) While this

might have been a "good deterrent" for "early" addicts, the researchers concluded that "hardcore addict[s]" would "still continue to abuse the product." (A5304.)

Stymied by the limitations of these conventional approaches, Purdue's scientists tacked to a counterintuitive course: combining the API with a gelling agent that would cause powder from a crushed tablet, when exposed to liquid, to become viscous and deter abuse.[1] The prior art suggested this approach would fail to deliver controlled-release doses of oxycodone to legitimate users: Gelling agents had been used in the prior art since at least 1975 in an attempt to deter abuse, but were combined with drugs in immediate-release formulations, not controlled release. (A6196-6202.) Indeed, the prior art explicitly recognized the concern that gelling agents would disrupt the intended controlled-release profile: the 1995 Bastin reference expressly discouraged combining gelling agents and drugs with a release profile that must be carefully controlled, identifying the "serious deterioration of drug release" as a "disadvantage" of a gelling-agent-plus-drug combination. (A79490 (5:29-36); A79513 (28:18-22); A4487-89; A6198-6200; A6218-19.) Moreover, the prior art did not quantify the level of viscosity required to deter abuse, instead specifying, *e.g.*, just enough gelling to trap the drug in a filter prior to injection; none taught quantitative viscosity levels necessary to

[1] As another, complementary mechanism, Purdue also explored crush resistance.

hinder pulling the gelled formulation into a hypodermic needle.[2] (A75; A6194.) And, none of this art disclosed any quantitative viscosity necessary for achieving a balance between deterring abuse but not disrupting or "deteriorating" the controlled release of the drug when taken as intended to achieve a 12-hour therapeutic effect.

For OxyContin®'s carefully controlled release that provides a 12-hour therapeutic effect (*e.g.*, easing pain to allow patients to sleep through the night), that kind of disruption could leave patients without sufficient pain relief during the 12-hour period. (A4488.) Purdue was well aware of this known risk, *i.e.*, that gelling agents could "retard further the release profile of the oxycodone active substance." (A5305; A5316; *see also* A4568 (effective release of oxycodone "is a pretty important concern in terms of the patient").) In fact, Benjamin Oshlack, the highly experienced Purdue formulator and co-inventor of the '888 patent who first thought to use gelling agents for an abuse-deterrent formulation of OxyContin®, had for this reason never before tried to use gelling agents to deter abuse. (A5305.)

Purdue's scientists and their research colleagues thus began from scratch. Mr. Oshlack and Drs. Curtis Wright and Christopher Breder (medical doctors at

[2] Abusers sometimes used cotton or other filters when syringing in an attempt to rid the injected material of particulates. (A2877-79; A4627-29; A6194-6203.)

Purdue) bucked the conventional wisdom and, after "a lot of brainstorming sessions" (A62272-73), began work to make gelling agents into an effective abuse-deterrent mechanism for the controlled-release oxycodone medication. (A5304-06; A62283-85.) They started "looking at several gelling agents and … their properties in abuse models" to quantify how viscous the dissolved dosage form needed to be to resist pulling into an abuser's needle (or to deter abuse from snorting)—while still maintaining the controlled-release profile and 12-hour therapeutic effect. (A5306; A62293-94.)

The Purdue scientists tested gelling agents like xanthan gum, pectin, and sodium alginate to determine how best to turn the controlled-release oxycodone formulation into a gel when abused, but not disrupt its release or its 12-hour therapeutic effect when taken orally as intended. (A138-39; A5306-13.) By focusing on how abusers would try to abuse the dosage form, they experimented with precisely how viscous the gelled solution had to be to resist pulling into needles in preparation for injection (or to resist absorption from snorting into moist nasal passages) and identified specific levels of viscosity that would achieve that effect. (A5304-06; A62296-97 (a goal was a material "so gunky so that you couldn't suck it into a syringe"; also, "[o]ne can only imagine snorting jelly" and getting "this goo [stuck] in your nasal passages").) The scientists "conclu[ded] that about 10 centipoise viscosity would make injectability difficult." (A5306-13;

A139 (Table 3).)[3] And at 60 cP, they found, the effect was even greater—attempts to syringe the gummy mass "picked up large pockets of air," which showed that the solution was even more difficult to pull into a syringe. (A139 (Table 3).) To achieve these goals, the Purdue formulators settled on PEO as the gelling agent because it achieved bioequivalence with the release profile of original OxyContin® yet contributed the appropriate viscosities for abuse deterrence. (A3031-32; A5414.)

Ultimately, Purdue achieved its goal: a controlled-release oxycodone formulation that deters abuse by imparting a specific amount of viscosity to the formulation when tampered with by dissolution, yet retains the controlled-release properties of original OxyContin® that provide a 12-hour therapeutic effect when taken as intended. (A2946; A5305; A5316-19.)

In an August 2001 provisional application and in continuation applications thereafter, the Purdue scientists claimed their inventive combination of features. (A121.) The '888 patent issued on December 25, 2012, and claims the August 2001 priority date. (A121.)

Claim 1, from which all of the asserted claims depend, recites:

A controlled release oral dosage form comprising:

[3] The more "viscous" a liquid is, "the greater its resistance and the more force needed to make it flow"; viscosity is measured in centipoise (cP). (A44-45.)

> from about 2.5 mg to about 320 mg oxycodone or a pharmaceutically acceptable salt thereof; and
>
> a gelling agent comprising polyethylene oxide in an effective amount to impart a viscosity of at least about 10 cP when the dosage form is subjected to tampering by dissolution in from about 0.5 to about 10 ml of an aqueous liquid;
>
> the dosage form providing a therapeutic effect for at least about 12 hours when orally administered to a human patient.

(A143 (40:22-32).) Claim 7 depends from claim 1 but requires a viscosity of "at least about 60 cP." (A143 (40:51-52).)

In allowing the '888 claims, the patent examiner explained: "The prior art does not teach or suggest the claimed invention as a controlled release dosage form comprising a drug susceptible for abuse (here as oxycodone) that also comprises a gelling agent to impart the viscosity unsuitable for injections or nasal administrations when the dosage form is subjected to tampering by dissolution." (A108476-77; A108447.) All of the types of prior art relied upon by the district court, including most of the specific references it cited, were presented to the examiner. (A121-23 & A135-37 (22:50-25:37) (citing all of the "gelling" art other than Joshi; citing PEO art including McGinity, Royce, and OROS formulations, of which the '591 application, although not cited, is an example).)

D. Reformulated OxyContin®'s Success

1. Regulatory Approval And Acknowledgement Of The Reformulation's Abuse-Deterrent Features

Reformulated OxyContin®, which has the same API as original OxyContin® and retains the original formulation's effective pain relief over 12 hours, is nonetheless fundamentally different from original OxyContin®, because of the incorporation of abuse-deterrent properties, including gelling properties such as those that ripened into the '888 patent. (A2946; A2970-71; A5417; A5435-38; A43949.) In November 2007, Purdue filed an NDA for Reformulated OxyContin®. (A2953; A44177.)

FDA initially was not persuaded that Reformulated OxyContin®'s new abuse-deterrent mechanisms would actually deter abuse, and in 2008, it asked Purdue for in-depth testing and data. (A3036-38; A46045-50.) After consulting with experts on drug abuse and tampering approaches (A3038), Purdue conducted rigorous *in vitro* tests designed to simulate a comprehensive range of abuse scenarios, including dissolving crushed tablets in varied amounts of liquid, heating the extract, and trying to pull it into needles of various sizes. (A121 (1:19-31); A126 (5:31-36); A127 (7:28-34); A139 (32:27-39); A5414-21; A6250-51; A44489-92; A45843-44; A45876-83; A86123-26.) These studies showed that Reformulated OxyContin®, while retaining its efficacy for legitimate use, outperformed the original formulation in every abuse simulation tested. (A3048.)

Among other things, Reformulated OxyContin®, when crushed and mixed with water, formed a viscous gel that resisted passage into insulin and other fine-bore needles typically used by abusers, as well as even larger-diameter needles neither generally available to the public nor appealing to abusers. (A5416-24; A61715.)

Based on these tests, FDA approved Reformulated OxyContin® in April 2010. (A3048; A44177-82.) After preparing the new product for sale, and based on its belief that the reformulation would help to reduce OxyContin® abuse and the harmful consequences, Purdue ceased selling original OxyContin® in August 2010 and sold only Reformulated OxyContin® thereafter. (A3049; A44839.) Reformulated OxyContin®, although it largely eliminated illegitimate use, earns approximately $2 billion annually—a "blockbuster" success. (A3291-96; A3312-16; A5427-29; A5533-37; A5972-74; A47454; A61778-79; A61848.)

Nonetheless, even after approving Reformulated OxyContin®, FDA was hesitant to allow Reformulated OxyContin®'s label to reference its abuse-deterrent features. (A60; A2897; A3050-53.) To convince FDA, Purdue conducted extensive post-marketing epidemiological and "liking" studies (clinical studies of abuser reactions to the reformulated product) to evaluate the real-world effectiveness of its new product in reducing abuse. (A44296-44319; *see also* A3050-54.) The findings "indicate[d] that replacement of the original formulation

of OxyContin with the reformulated version has resulted in a decrease in misuse and abuse." (A44303-04.)

On April 16, 2013—three years after it approved the new drug—FDA found, based on Purdue's studies, that Purdue had withdrawn original OxyContin® for safety reasons. FDA based its decision in part on the gelling properties of the reformulation: The data showed that, when compared to original OxyContin, "the benefits of the original OxyContin no longer outweigh its risks." (A44842-43; *see also* A3052-54; A3288-90.) Specifically with respect to the gelling properties, FDA found the data showed that, "when subjected to an aqueous environment, reformulated OxyContin gradually forms a viscous gel." (A44842.) Accordingly, FDA concluded "that the physicochemical properties of reformulated OxyContin are expected to make abuse via injection difficult and are expected to reduce abuse via the intranasal route." (A44842.) Based on these findings, FDA refused to approve generic versions of original OxyContin®. (A44837-48.) Refusal of a generic version is a significant step for FDA; it took that step for OxyContin® only because it was convinced that Reformulated OxyContin® offered a genuine improvement in "safety." 21 C.F.R. § 314.162(a)(2).

The same day, and also based on Purdue's studies, FDA approved supplemental labeling for Reformulated OxyContin® that describes its abuse-deterrent properties, *i.e.*, that it has physical and chemical properties "expected to

make abuse via injection difficult" and "expected to reduce abuse via the intranasal route." (A44262-95 at A44282; A44813-36.) Reformulated OxyContin® was the first opioid with FDA-approved abuse-deterrent labeling. (A5486.) Endo unsuccessfully sought abuse-deterrence labeling for reformulated Opana® ER, its controlled-release formulation of a different opioid. (A2896; A3323-26; A4498; A5540-41.)

2. Reformulated OxyContin®'s Commercial Success

FDA's decision recognizing Reformulated OxyContin®'s abuse-deterrent properties transformed the market for controlled-release oxycodone. If FDA had not determined that original OxyContin® was withdrawn for safety reasons (because the reformulation was safer yet equally effective), less expensive generics of that original formulation would have flooded the market, sales of Reformulated OxyContin® likely would have plummeted, and abuse would have increased again, costing many lives. (A3322-25; A5540-47.) For instance, one of Defendants' experts conducted studies showing that, when branded and generic drugs compete, the branded drug generally loses 50 to 70 percent of its market share within a year. (A5968.) Given its abuse-deterrent technologies as recognized by FDA, however, only Reformulated OxyContin® can serve the market need for controlled-release oxycodone medicine. (A5548.)

The very different market experience of Opana® ER shows the enormous contribution that Reformulated OxyContin®'s effective abuse-deterrent properties have made to its commercial success. Endo petitioned FDA to determine that its reformulated Opana® ER product has abuse-deterrent properties that warrant prohibiting generic sales of the original drug. (A5540-42.) Unlike for Reformulated OxyContin®, however, FDA found Endo's showing unconvincing and denied the petition. (A5541.) The consequences are telling: Just three months after generic competition to the controlled-release oxymorphone formulation entered the market, reformulated Opana® ER's sales dropped by 28 percent. (A5541-42.)

E. The District Court Proceedings

This case arises under the Hatch-Waxman Act. 21 U.S.C. §§ 301 *et seq.* After Amneal filed an ANDA seeking FDA approval to market generic versions of Reformulated OxyContin®, Purdue sued Amneal and another defendant, Teva, for infringement of the '888 patent as well as a second patent asserted against Teva. At a five-day bench trial in 2014, the parties adopted, as part of that record, a 2013 bench trial from an earlier Teva case involving other patents that cover

Reformulated OxyContin®. (A32.) Before the court issued its rulings on the 2014 trial, Purdue and Teva resolved their disputes in this case.[4] (A34.)

Against Amneal, Purdue asserted claims 5, 7, 23, and 24 of the '888 patent. Each asserted claim limits claim 1 in certain respects. Claim 5 specifies that "the aqueous liquid is water." (A143 (40:45-46).) As noted above, claim 7 requires enough gelling agent to impart "a viscosity of at least about 60 cP." (A143 (40:52-53).) Claims 23 and 24 are multiple dependent claims that each depend from at least claims 5 and 7, and each specifies that the claimed viscosity is imparted when certain tampering conditions occur. For claim 23, the claimed viscosity occurs when the dosage form is tampered with "by crushing and dissolution in the aqueous liquid," and for claim 24, when the dosage form is tampered with "by dissolution in the aqueous liquid with heating greater than 45° C." (A144 (42:10-17).) For purposes of the asserted claims, the parties agreed that a "person of ordinary skill in the art has a degree in one or more fields of medicine, chemical engineering, chemistry, pharmaceutical science, polymer chemistry, pharmaceutics, pharmaceutical technology, pharmacokinetics, and/or pharmacology, and/or a number of years of industry training or experience in one or more of those fields." (A70 (citing A6288-89).)

[4] For ease of reference, at times Purdue's briefs on appeal may refer to Amneal alone when referring to evidence presented by either or both Defendants.

1. The Court's Determination that Amneal Infringes All Asserted Claims

As an initial matter, after construing the claims, the court found that all of Amneal's accused dosage strengths met all the limitations of, and thus infringed, all of the asserted claims, including the higher 60 cP viscosity limitation of claim 7. (A43-48; A62-66; A61409-15.)

2. The Court's Obviousness Determination

In rejecting Amneal's anticipation defense under 35 U.S.C. § 102, the court recognized that "no single prior art reference discloses an abuse-deterrent controlled release oxycodone dosage form containing the gelling agent PEO." (A83; *see also* A77 (the '888 patent "may be the first patent to disclose in detail controlled release dosage forms that utilize gelling agents to deter abuse").) Nonetheless, the court held it would have been obvious to combine a controlled-release form of oxycodone with a gelling agent, relying on a combination of various prior-art references directed to formulations that either were already before the PTO or are cumulative thereof. (A70-85.)

a. "Gelling" References

Before the innovation of Purdue's '888 patent, gelling agents had never been utilized to prevent abuse of any controlled-release drugs, much less opioids or oxycodone. The reason for that is simple: The prior art, as well as those of ordinary skill, knew and expected that gelling agents would disrupt the controlled-

release profile of drugs and affect efficacy when taken by legitimate, non-abusing pain patients.

The prior art differed from the '888 inventions in many ways. None of the art disclosed a particular length of therapeutic effect for their dosage forms. Nor did any disclose testing viscosity by replicating how addicts typically abuse OxyContin®. And, none disclosed levels of gelling sufficient to prevent uptake into or injection from a hypodermic needle without filtering; certainly, none disclosed the '888 patent's quantitative viscosity levels (either 10 cP or 60 cP).

Shaw, a U.S. patent filed in 1975 (A77481-85), was the earliest of the prior-art references relied on by the court. Shaw addressed deterring a method of abusing methadone that is "totally different" from how addicts abuse OxyContin® (A5351); Shaw's method of abuse involved dissolving the tablet in at least 12 times as much water, and filtering, evaporating, and concentrating the extract. (A77482 (1:44-56).) Shaw disclosed "incorporating … an ingestible solid having thickening properties which causes rapid increase in viscosity upon concentration of an aqueous solution thereof" in order to "prevent injection abuse" of drugs used to treat narcotic addiction. (A77481 (Abstract).) The dosage forms disclosed in Shaw were immediate-release tablets, not controlled-release ones. (A6196; A77482 (1:30-35); A77483 (4:64-67).) And Shaw presumed that abusers would filter the aqueous solution before injecting; indeed, the unfiltered solution could be

syringed. (A77484 (5:41-48).) Thus, Shaw did nothing to (i) deter abuse of unfiltered solutions, or (ii) address how to use gelling agents to allow for the controlled delivery of oxycodone or other pain medication or a 12-hour therapeutic effect.

Hoffmeister, another U.S. patent filed in 1975 (A82784-89), disclosed the incorporation of nontoxic water-gellable materials in combination with "medicinal agents having parenteral abuse potential," thereby rendering such pharmaceutical compositions resistant to "aqueous extraction," *i.e.*, suitable for parenteral (non-oral) injection. (A82784 (Abstract).) Hoffmeister, too, assumed that abusers would filter the aqueous solution (A82785 (1:65-2:8) ("sufficient to form a gel with substantially no *filterable* liquid")); all of its tamper testing utilized filters. (A82786 (Table 1).) Although the medicines identified in Hoffmeister included certain opioids, Hoffmeister did not disclose oxycodone or any controlled-release formulations. (A82785 (1:36-40); A6197.) Hence, Hoffmeister, like Shaw, taught nothing regarding (i) deterring abuse without filters, or (ii) the use of gelling agents in oxycodone formulations with controlled release or a 12-hour therapeutic effect.

The 1995 **Bastin** application (A79484-79522) taught the ordinary artisan that combining a gelling agent with the active drug in a formulation could adversely interfere with the drug's release profile. Three aspects of Bastin show this. *First*, Bastin expressly called out this release problem when criticizing

Hoffmeister: Under Hoffmeister's approach, "wherein the drug with potential for abuse is mixed with the gelling agent," the combination "is liable to seriously retard the release of the drug substance," *i.e.*, cause "a serious deterioration of drug release." (A79486 (1:22-29); A79513-14 (28:18-29:15).) Bastin disclosed a test of the combination, in which "only 50% of the drug" was released after two hours, and the remaining drug was "trapped in the tablet matrix." (A79513 (Table 4 & 28:18-22).) *Second*, Bastin taught that, to avoid this "disadvantage" and allow for release of the drug when taken intact, one would have to "reduc[e]" the gelling agent to such a degree that any "abuse resistance potential of the tablet" would be "severely limit[ed]." (A79490-91 (5:32-6:2).) Bastin thus taught that limiting its gelling effect to what was necessary to be trapped in a filter was adequate. (A79509-10 (Test 1).) In other words, Bastin taught that including amounts of gelling agents sufficient to resist abuse of controlled-release products would disrupt the carefully calibrated release of a drug—an attribute critical to controlled- and extended-release formulations such as OxyContin®. *Third*, Bastin's solution to the release issue was a "layered" approach, such that the gelling agent and the active ingredient would not be intermixed. This was so that "release of drug can proceed relatively uninhibited and substantially similar to that of conventional tablets which do not possess a gelling layer." (A79490 (5:24-27).)

Finally, the 2001 **Joshi application** (A78438-51; A86659-64), the only one of these references not expressly identified in the '888 patent (A124; A6158-59), disclosed adding a gelling agent to immediate-release chewable formulations of central nervous system stimulants such as Ritalin®. (A6200-02; A78445-46 (Examples 1-2); A86662 (Example 1).) Joshi did not address controlled-release formulations; did not address central nervous system *depressants* such as analgesics, opioids, or oxycodone; and did not disclose any tests to evaluate abuse deterrence or requirements for the viscosity of its dosage forms.[5] As with all of this art, Joshi said nothing about how to use gelling in any controlled-release formulation, much less the quantitative level of viscosity necessary to simultaneously deter abuse and permit a 12-hour therapeutic effect.

b. PEO References

The court also relied on prior art that it found disclosed or taught PEO, concluding that it has gelling properties that affect release. (A73-77; A82; A6308-19 (McGinity or the '963 patent); A45595-99 (Zhang dissertation); A78438-51

[5] There are two related Joshi applications. The Joshi provisional application (A78437-51) was filed only three months before the '888 patent application, and the later Joshi application (A86659-64) was filed shortly after. They are largely identical, and neither supports the court's ruling. For instance, while the later Joshi application states that "[g]el formation occurs" when the tablet is added to 1 mL of water, neither application tested viscosity or mentions syringes or needles. (A6200-01; A86662 (¶ 42).) Also, the later application suggests that gelling occurs *in the skin* only *after* the material is injected—far from the approach taken by the '888 patent, which deters injection in the first place. (A86660 (¶ 9); A6201.)

(Joshi provisional application); A79484-79522 (Bastin); A83985-91(Royce); A86630-58 (McGinity and Zhang application); A86659-64 (Joshi application); A108504-60 ('591 application); A108877-84 (PolyOx article).) Other than Joshi and Bastin (already discussed), none of this art had anything to do with using PEO to deter abuse, and, like all of the "gelling" art, none of this art addressed the conundrum of how to use PEO to deter abuse without interfering with controlled and extended release of tablets taken as intended, much less any particular viscosity levels for achieving that balance.[6] Indeed, "OROS" formulations that used PEO as part of a controlled-release pharmaceutical formulation (which worked, roughly, by using osmotic pressure to push the active ingredient from the capsule through a tiny hole) had been in use for a decade or more by 2001, and yet no one had suggested using its PEO to deter abuse. (A6161-63.) The '888 patent explicitly cited OROS formulations to the examiner. (A135-37 (22:50-25:37).)

* * * *

Despite all of these differences and teachings away from the '888 inventions, the court held that one skilled in the art would have been motivated to combine the features of various references, and add new ones (such as the specific viscosity levels), to arrive at the '888 patent. (A81-85.)

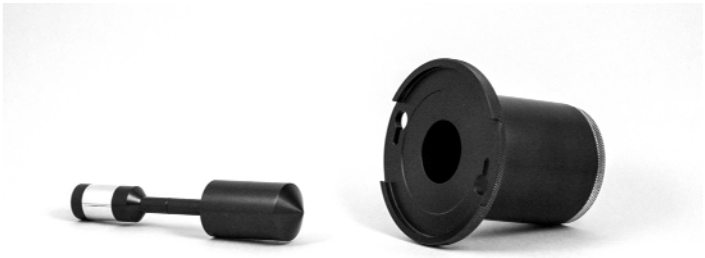
[6] Also, as the court found, Bastin did not expressly disclose PEO. (A77 n.14.)

3. The Court's Determination That Claim 7 Is Indefinite

The court waited until after trial to address Amneal's argument that the claims did not sufficiently define "the method an ordinarily skilled artisan would use to assess whether the 10 cP viscosity limitation" was met—the so-called "viscosity test." (A43; *see also* A5-6.) The court found that one of ordinary skill would need to know certain parameters for measuring viscosity, and that, although the parameters were not exact, the patent sufficiently defined the temperature at which the dissolved dosage form is tampered with, the temperature at which it is tested (*i.e.*, administered by the abuser), and the extent to which the dosage form is dissolved. (A49-54.) In finding sufficient guidance for the parameter of testing (administering) temperature, the court recognized the "direction" offered by both "common sense" and the specification's focus on deterring abuse. (A50-51.) Specifically, the court determined that the claimed testing temperature did not extend to temperatures "at or near boiling" because "[a]n ordinarily skilled artisan would understand as a matter of common sense" that "abusers do not inject, snort, or swallow extremely hot liquids." (A50-51.)

As relevant here, the court also found that the ordinary artisan would expect the patent to disclose a fourth viscosity-testing parameter—"shear rate." (A48; A86-87.)

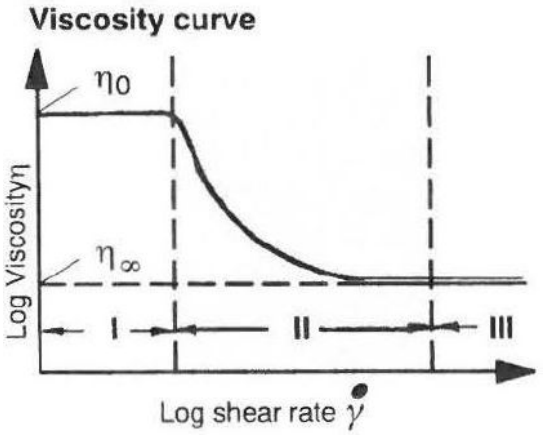
Viscosity is measured using a piece of laboratory equipment called a rheometer. (A5863; A5908; A61922.) As shown in the following photograph of equipment used by Purdue's expert, a rheometer features a cup and a spindle that fits snugly inside the cup.



(A5614-15; *see also* A108975-78.) The cup is filled with the material being tested, the spindle is then rotated inside the cup, and the rheometer measures the material's resistance to the spindle's turning. (A5615.) The greater the material's resistance, the higher its viscosity. (A5615.) To calculate viscosity, one takes into account "shear rate," which is the speed of the spindle rotation divided by the distance between the spindle and the edge of the cup, and which is expressed in a unit of measure called "reciprocal seconds." (A45; A61920.)

The viscosity of some materials, like oil or water, is not affected by changes in shear rate; these so-called "Newtonian liquids" maintain the same viscosity regardless of shear rate, *e.g.*, regardless whether the rheometer is adjusted to rotate the spindle faster or slower. (A61923.) However, shear rate can affect the viscosity of non-Newtonian liquids, including the "pseudo-plastic" gelling

materials (like PEO) claimed in the '888 patent. (A6183-84.) This characteristic, and the "classic" curve shape of viscosity levels of pseudo-plastic materials, was well-known in the art. (A5616; A5620.) A depiction from Schramm, a standard rheology textbook, is reproduced here:



I: First Newtonian range → viscosity η_0 not yet dependent on shear rate.
II: In this range viscosity drops as a result of molecular or particle orientation.
III: Second Newtonian range → viscosity η_∞ stays constant, independent of further increases of shear rate.

(A61924-25; *see also* A45-46; A5616; A5620; A5685.)

Within a range of very low shear rates—the region denoted "I" in Schramm's figure—pseudo-plastic liquids behave like Newtonian liquids; their viscosity is independent of fluctuating shear rates. (A61924.) This range of very low shear rates is known as a material's "zero shear" region. (A61924.) Schramm identifies and describes this region in detail. (A61924-25.) Because a material's viscosity within its zero-shear region provides a viscosity measurement that is not dependent upon shear rate, the zero-shear region reflects the material's viscosity at

rest. (A45-46; A5616-20; A6184-85; A6279.)[7] Finding and testing a material's viscosity within the zero-shear region is taught in textbooks like Schramm and is standard practice in the pharmaceutical industry. (A5615-17; A6183-86; A61924.)

When the spindle spins faster, a pseudo-plastic material's viscosity begins to depend on shear rate, decreasing on a curve as shown in the region denoted "II" in Schramm's figure reproduced above. Eventually, at "extremely high shear rates," the viscosity of the material again plateaus with viscosity independent of shear rate. (A45; A5615-20; A6183-86; A61924-25.) This is depicted in the region denoted "III" in Schramm's figure.

As Purdue explained in the district court, one of ordinary skill in the art at the time of the '888 inventions would have known that the pseudo-plastic dosage forms disclosed in the '888 patent would exhibit the same type of viscosity curve depicted in Schramm. (A138-43.) For a skilled artisan, the '888 patent provides ample guidance regarding which shear-rate range to use for the viscosity test. (A124 (2:18-20); A125 (3:5-36); A139 (Example 3).) The patent aims to deter abuse by "decreasing the 'attractiveness' of the dosage form to a potential abuser" (A124 (2:46-47)), and it does so by making a tampered-with formulation "thick and viscous" when crushed and mixed with aqueous liquid, in turn making the

[7] Measuring the viscosity of a material while it is truly *at rest* is impossible because viscosity is a measure of a material's resistance to *movement*. (A61923.)

formulation "difficult[]" to "inject" (or "stick to the nasal passage and minimize absorption"). (A125 (3:5-36); A139 (Example 3).) Because the zero-shear region most closely approximates the static state of the dissolved drug when an abuser is preparing to inject it (or when it is in an abuser's nose), one skilled in the art would locate that region and measure the material's viscosity there. (A5615; A6183-84.)

The court, however, held that the claims are "not confined to zero shear." (A48.) Instead, the court found, the ordinary artisan could "reasonably measure viscosity across a broader range of shear rates." (A48.) The court could not "ascertain the precise boundaries of the … range" the artisan could reasonably use, but based on the shear rates that both Purdue's and Defendants' experts used, the court concluded that the artisan could use a range of at least .01 to 100 reciprocal seconds. (A44-48; A85-87.)

Based on that construction, the court determined that claim 7 was indefinite. Claim 7 requires the tampered-with dosage form to reach at least about 60 cP viscosity. (A143 (40:51-52).) When tested at shear rates within the court's range, "all … of Amneal's tablets achieved viscosities well above 60 cP," which was sufficient evidence to find that Amneal infringed claim 7 (and all other asserted claims). (A63-64; A5625-26; A61409-15.) All of Teva's tablets achieved viscosities above 60 cP within that range as well. (A5623-24; A61491-97.) However, the viscosity of one of Teva's (but not Amneal's) dosage strengths

dropped below 60 cP viscosity when tested beyond zero shear up to 100 reciprocal seconds. (A85-86.) On that basis, the court concluded that shear rate "directly impacts the results of the viscosity test and therefore the determination of infringement [of claim 7]," and since, in the court's view, "the patent does not tell an ordinarily skilled artisan how to select shear rate," the court deemed claim 7—but only claim 7—indefinite. (A91; *see also* A64; A61491-97.)

SUMMARY OF ARGUMENT

I. The asserted claims disclose a novel and nonobvious combination of features deserving of patent protection: a controlled-release oxycodone dosage form that includes a PEO-containing gelling agent that imparts a specified level of viscosity (at least about 10 cP or about 60 cP) when the dosage form is tampered with and mixed with liquid—but does not disrupt the drug's 12-hour therapeutic effect. The prior art failed to teach or suggest all of the claim limitations, particularly the claimed viscosity limitations. In fact, although using gelling agents to deter abuse of immediate-release drugs had been known in the prior art for over 25 years, the prior art taught away from using gelling agents together with a drug, like OxyContin®, that requires a carefully controlled release profile. The prior art had long understood, and the Bastin reference explicitly taught, that gelling agents would disrupt a drug's release profile.

The district court failed to appreciate differences between the prior art and the '888 patent, coming to the wrong conclusion because it relied on improper hindsight analysis. Rather than looking for reasons to support whether a person of ordinary skill in the art at the time of the '888 inventions would have been motivated to make the first-ever gelling-plus-controlled-release formulation, the court retraced the path of the inventors to select and combine those features. That was legal error. A focus on the viscosity limitations confirms this. With none of the prior art teaching the use of a gelling agent in a controlled-release formulation, necessarily none taught that any particular quantitative viscosity level mattered for a controlled-release dosage form. The court erred in overlooking the nonobvious balance struck by the '888 patent between abuse deterrence and controlled release that achieves a 12-hour therapeutic effect.

Objective indicia, which are independent and especially probative evidence of nonobviousness, also show that the '888 inventions were nonobvious. Reformulated OxyContin®, which is covered by the '888 patent, fundamentally altered the market for controlled-release oxycodone. But for the reformulation's abuse-deterrent features and its 12-hour efficacy, FDA would have allowed generic versions of original OxyContin® into the market, and sales of Reformulated OxyContin® would have plunged. Further, FDA did not allow Purdue to include the abuse-deterrent features of Reformulated OxyContin® in its labeling until data

indicated that the reformulation reduced abuse. As these actions recognize, Reformulated OxyContin® addressed the opioid-abuse problem, which rose to prominence in the 1990s and reached epidemic proportions by the early 2000s. The district court erred by misunderstanding, or in some instances believing it could not consider, this strong objective evidence of nonobviousness.

II. The district court also erred in finding claim 7 indefinite based on a construction that the patent had to specify a shear-rate range in order to sufficiently define the claim. An ordinarily skilled artisan would understand from the claims and specification that viscosity must be tested in the dosage form's zero-shear region, because that region most closely approximates the static state of the dissolved drug when an abuser is preparing to inject it (or after the powder is snorted and moistened by the nasal cavity). The court improperly rejected the straightforward and undisputed intrinsic evidence to that effect, and misinterpreted the extrinsic evidence as well. Further, even under the court's construction that an ordinary artisan would read the patent as encompassing a wide range of shear rates encompassing the zero-shear region and beyond, the claim's scope is reasonably certain. No expert used shear rates beyond the court's wide range, and the court's construction had no effect on its ability to find that Amneal infringes all of the asserted claims, including claim 7. Any theoretical uncertainty about an ultimate limit of the shear-rate range does not render that claim indefinite.

STANDARDS OF REVIEW

Obviousness and indefiniteness are questions of law reviewed *de novo*, with underlying factual findings reviewed for clear error. *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1351 (Fed. Cir. 2010); *ePlus, Inc. v. Lawson Software, Inc.*, 700 F.3d 509, 516 (Fed. Cir. 2012).

Claim construction is a question of law reviewed *de novo*. The district court's analysis of the intrinsic evidence is also reviewed *de novo*, while subsidiary fact findings regarding extrinsic evidence are reviewed for clear error. *Teva Pharm. USA, Inc. v. Sandoz Inc.*, 135 S. Ct. 831, 841 (2015).

ARGUMENT

Using gelling agents with the intent to deter abuse of immediate-release drugs by injection had been known since at least 1975. But, in the face of skepticism and at least one express teaching away in the prior art, Purdue's 2001 combination of gelling agents with controlled-release, 12-hour-therapeutically-effective oxycodone formulations was a patentable, inventive leap forward. Indeed, it has helped abate an abuse epidemic. The nonobvious inventions of the '888 patent deserves patent protection not just for the manifest good that it does for the public, but also because it overcame doubts and prior art that taught away from that solution. The '888 formulations are also sufficiently defined.

I. THE CLAIMS OF THE '888 PATENT WERE NONOBVIOUS

A claim is invalid under § 103 only if the challenger shows, by clear and convincing evidence, that "the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a) (now § 103). The factual inquiries underlying that legal issue include determining (1) "the scope and content of the prior art"; (2) "the differences between the prior art and the claims at issue"; (3) "the level of ordinary skill in the pertinent art"; and (4) any relevant secondary considerations, such as "commercial success, long felt but unsolved needs, failure of others, etc." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

If the prior art does not teach a claim limitation, that difference can render the claims not obvious. *See August Tech. Corp. v. Camtek, Ltd.*, 655 F.3d 1278, 1290 (Fed. Cir. 2011). Even where the prior art contains all of the claim limitations, the challenger must still show by clear and convincing evidence "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). "[T]he showing of combinability …

must … be 'clear and particular," *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1348-49 (Fed. Cir. 2000), and the court should make its analysis "explicit." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); *see also InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014) ("A reason for combining disparate prior art references is a critical component of an obviousness analysis."). If, on the other hand, "the prior art indicated that the invention would not have worked for its intended purpose or otherwise taught away from the invention," the "opposite conclusion" should follow—the invention is nonobvious. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009).

The court legally erred in concluding that one of ordinary skill in the art would have been motivated to combine those elements into the '888 patent's gelling-plus-controlled-release-plus-12-hour-therapeutic-effect inventions. The prior art did not disclose all of the claim elements. Even if it had, the prior art did not teach or suggest the '888 inventors' approach. Indeed, that art discouraged the ordinary artisan from adding gelling agents to a formulation that had to maintain a carefully controlled release profile to achieve a 12-hour therapeutic effect for the active drug. The court reached the contrary conclusion only by way of improper hindsight.

The court also legally erred by holding that the quantitative viscosity limitations of the asserted claims were obvious from the prior art. The prior art does not teach any specific viscosity limitations for an abuse-deterrent gelling formulation, whether the threshold of at least about 10 cP or, as in claim 7, the greater threshold of at least about 60 cP.

A. The Prior Art Taught Away From Combining Abuse-Deterrent Gelling Agents With A Controlled-Release Oxycodone Formulation

Effectively combining gelling agents with a controlled-release drug to make the '888 inventions was not obvious in 2001. The prior art affirmatively and explicitly discouraged one of ordinary skill from adding gelling agents to a drug product that required a carefully controlled release profile. It was no small thing that the '888 patent was, as the court acknowledged, "the first patent to disclose in detail controlled-release dosage forms that utilize gelling agents to deter abuse." (A77.)

1. The Prior Art Taught Away From The '888 Inventions

The prior art taught away from the claimed combination. A person of ordinary skill would not have looked—and for over 25 years did not look—to gelling agents as a way to deter abuse of controlled-release drugs. In fact, the prior art warned against such a combination. Up to the time of the '888 inventions, opioid formulators were instead considering adding antagonists and different

physical agents (such as bittering agents or dyes) to deter abuse. (A2887-91; A4487-89; A5302-04; A45066-67.)

The '888 inventors' decision to try gelling agents (PEO or otherwise), and their insight that they could work in a controlled-release formulation with a 12-hour therapeutic effect that also deters oxycodone abuse, went against the grain of the prior-art teachings. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (an inventor's "willingness to confront and overcome obstacles" "cannot be discounted"). OxyContin®'s 12-hour therapeutic effect and controlled-release profile were (and remain) critical features for patients suffering from around-the-clock pain; those had to be maintained in any abuse-deterrent reformulation. (A5435-36.) The four pieces of gelling art cited by the district court (Shaw, Hoffmeister, Bastin, and Joshi) offered no assurance—but plenty of doubt—that gelling agents could be added to a formulation like OxyContin® without disrupting its carefully calibrated 12-hour therapeutic effect. Indeed, none of Shaw, Hoffmeister, or Joshi taught controlled-release formulations—much less controlled-release oxycodone formulations, or, even further afield, controlled-release oxycodone formulations having a 12-hour therapeutic effect. (A6196-97; A6200-02; A77482 (1:30-35); A77483 (4:64-67); A78445 (Example 1); A78446 (Example 2); A82785 (1:36-40); A86662 (Example 1); *see also* A5319-21 (describing the difficulties involved in achieving a 12-hour controlled-release

profile for oxycodone).) And although Bastin disclosed a sustained-release coating and materials "intended for the modification of release characteristics of the drug" (A79490 (5:1-13)), it explicitly warned about the "disadvantage" from the "serious deterioration" of the release profile that would be brought about by combining gelling agents with the active drug, and it disclosed a test in which such a combination left half of the drug still "trapped in the tablet matrix" after two hours. (A79513 (28:18-22).) For that reason, Bastin took a fundamentally opposite approach from the '888 patent and taught "layer[ing]" the drug and gelling agent, so that they were physically separate from each another. (A79514 (29:13-15).) Bastin, moreover, also focused on immediate-release, not controlled-release, drugs. (A6197.)

In other words, given that the particularized 12-hour therapeutic effect and controlled-release requirement of OxyContin® had to be preserved, the risk of disrupting those mechanisms was reason enough to direct a person of ordinary skill away from incorporating the prior art's gelling references. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (per curiam) ("A reference 'teaches away' when it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant."); *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1361-62 (Fed. Cir. 2012) (references' explanations "that use of negative pressure on or

surrounding a wound is dangerous to the patient … amount[] to teaching away" from an invention that used negative pressure to "treat" or "facilitate the healing of" a wound); *Spectralytics, Inc. v. Cordis Corp.*, 649 F.3d 1336, 1343 (Fed. Cir. 2011) ("prior Swiss-style machines taught away from embracing vibrations to improve cutting accuracy because all prior machines improved accuracy by dampening vibrations").

2. The Court's Hindsight Assumption About Using Gelling Agents Is Not Supported By The Prior Art

The court found a motivation to combine the '888 inventions' features only by engaging in improper hindsight analysis. "Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1376 (Fed. Cir. 2002); *see also* 35 U.S.C. § 103(a) (the nonobviousness inquiry evaluates "the claimed invention as a whole").

Perhaps the most stark indication of the court's hindsight re-mapping of the inventors' path can be seen in the fact that using gelling agents to deter abuse had been known since at least 1975, but none of the cited prior art combined gelling agents with a controlled-release pharmaceutical to deter abuse. Indeed, the court recognized that the Purdue inventors were likely the first to have done so. (A77.) Yet the court never asked itself why this was the case. And it certainly never

articulated a reason why a person of ordinary skill in the art at the time would have been prompted to follow Purdue's contrarian path.

To reach its conclusion, the court pointed out that Bastin referred to a "sustained release coating" and "materials known in the art intended for the modification of release characteristics of the drug." (A77; A79490 (5:1-13).) But the coating in Bastin did not contain a gelling agent, and indeed Bastin was steadfast in insisting that the gelling agent be kept separate from the API. (A6197-98; A79490-91 (5:19-6:2).)

The court's only other use of Bastin was purely speculative. Pointing to Bastin's concerns about retardation of immediate-release gel-plus-drug formulations, the court made the scientific leap and assumption that, if gelling agents "retard the release of the drug" in an immediate-release formulation, gelling agents might actually be "well-suited to *controlled* release dosage forms." (A76-77.) The court's assumption had no basis in Bastin or in scientific fact, particularly with respect to the claimed inventions. The controlled-release profile of the '888 oxycodone formulations required a carefully calibrated 12-hour therapeutic effect, and based on the prior art, it was doubtful that gelling agents would be compatible with that requirement. (A5317-21; A6132-35; A61516-31 ('042 patent).) It was legal error for the court to speculate—with the benefit of hindsight—that an ordinary artisan would read what Bastin called a "disadvantage" of using gelling

agents in even immediate-release drug profiles (A79490 (5:31)) as turning into an advantage when combined with controlled-release profiles. Even an expert or person of skill in the art cannot show clear-and-convincing evidence of invalidity by resort to "unfounded speculation." *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1571 (Fed. Cir. 1997).

As another telling indicator of its hindsight analysis, the court pointed to two PEO references, the McGinity and Zhang application and the '591 application—the former of which "is essentially equivalent to" the subsequent McGinity patent that was before the examiner, and the latter of which was cumulative of OROS art that was, too—as a "strong starting point" for the ordinary artisan, and found that one would have been motivated to combine their disclosures with others with an expectation of success. (A76-77; A82.) Only through the use of hindsight could the court have overlooked the conundrum of using PEO as a gelling agent to deter abuse while simultaneously providing a controlled-release profile to achieve a 12-hour therapeutic effect. Indeed, the court reached its conclusion by expressly following the inventors' path. The court reasoned that, although neither reference was "directed toward the reduction of abuse potential," and no reference had suggested using their formulations in that way, ordinarily skilled artisans would have looked to such references anyway *because the '888 inventors themselves did*

so. (A82 ("In fact, the inventors relied on prior art concerning [PEO-based] OROS dosage forms … in the '888 Patent.").)

Such "reasoning" is "always inappropriate for an obviousness test," and it compels reversal here. *Ortho-McNeil Pharm.*, 520 F.3d at 1364. The inventors' path to discovering a solution cannot be used to show that the solution was obvious. *See* 35 U.S.C. § 103 ("Patentability shall not be negated by the manner in which the invention was made."). "[A]n inventor may look at the prior art differently than those before her, arrive at a novel and nonobvious insight, and submit a patent application that compiles the prior art findings that led her to the insight in such a way as to render obvious in hindsight what was wholly nonobvious at the time she filed her application." *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1328-29 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 420).

Finally, even where the district court purported to trace the path of an ordinary artisan, the court's discussion makes clear that the court instead worked backwards from the '888 patent. (A82.) For one, the court ignored that the inventors themselves were not sure that gelling agents would work in OxyContin®'s controlled-release formulation. (A5305; A5316.) For another, the court skipped over the other, more ordinary approaches to addressing opioid abuse at the time—in particular, the quite different pharmacological solution involving

antagonists that had been highlighted by the CPDD and which Purdue itself had spent years pursuing. (A5302-04; A5319; A45066-67.)

The court dismissed the CPDD paper as having "limited probative value" because it was not prior art or written by persons of ordinary skill. (A75.) But that paper was hardly amateur. The CPDD, then a seven-decade-old organization "serv[ing] a leadership role in the field of drug abuse," is comprised of members from the same disciplines as one of ordinary skill in the art in this case. (A70.) Dr. Sellers, one of Purdue's experts, is a member. (A2885.) That highly qualified group commissioned the taskforce that wrote the paper, which relied on numerous studies and other scientific references to reflect what abuse-deterrence strategies were actually being tried—none of which discussed gelling, as the court acknowledged. (A45058-59.) And as the court recognized, in fact no one achieved an abuse-deterrent-gelling controlled-release oxycodone dosage form, much less with its 12-hour therapeutic effect, before Purdue did so. (A77; A83.)

In short, only by using the '888 patent "as a guide through the maze of prior art references" could the court have ignored the rest of the body of art and assumed that ordinarily skilled artisans would zero in on the gelling references. *Grain Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988). That forbidden hindsight-based approach was legal error.

B. The Prior Art Did Not Teach Or Suggest The Quantitative Viscosity Claim Limitations

Even the court agreed that "the prior art does not disclose the quantitative level of viscosity that the gelling agent must produce." (A75.) Because the art gave no direction as to those critical limitations, that difference alone renders the '888 claims nonobvious. *See In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

1. The Claimed Viscosity Levels Are Critical Limitations

The viscosity levels specified in each of the asserted claims are critical because they represent threshold levels at which the formulation most effectively deters abuse yet still works throughout its full dosing period for legitimate pain patients. The '888 inventors determined that, after the tablet was crushed and mixed with a small amount of water to simulate what an abuser does, it became difficult to pull the resulting extract through an insulin syringe when it contained enough gelling agent to reach 10 cP viscosity. (A139 (Table 3); A5306; A108447; A108452; A108476.) At 60 cP, the material was even more difficult to syringe. (A139.)

The prior art on abuse-deterring gelling agents did not teach or suggest any quantified levels of viscosity of the formulation-turned-gel.[8] Joshi never even

[8] Indeed, for quantifying effectiveness, some of those prior-art references measured variables other than viscosity, such as the molecular weight of the PEO.

mentioned viscosity. Nor did Hoffmeister, which was instead directed to causing just enough of a gelling effect to prevent any liquid from passing through a filter—*i.e.*, preventing a "filterable liquid" from forming (A82785 (1:66-2:17 & 2:32-40))—thus assuming that abusers would try to draw the solution into a syringe through a cotton or other filter rather than pulling it up directly into the needle. (A6194-95; A6206-07; A6322 (1:34-37).) Bastin had the same focus on eliminating "filterable liquid" and never required a quantitative viscosity level for the gelled formulation. (A79489 (4:6-10).)[9] Finally, Shaw mentions viscosity only in the context of a method involving a large amount of water, filtering, evaporation, and concentration that is "totally different" from the tampering by dissolution discussed in the '888 patent—and does not quantify the viscosity required to deter abuse. (A5351; A77481 (Abstract); A77482 (1:44-56); A77482 (2:5-10); A77484 (6:3-25).)

By contrast, the '888 patent claims a formulation that sufficiently deters abuse in and of itself while maintaining the controlled release and 12-hour

(continued…)

(A6194-96; A6206-07; A77484 (6:3-21); A79484 (Abstract); A79486 (1:17-29); A79489 (4:1-6); A79511 (26:4-11); A82784 (Abstract); A82785 (1:66-2:17).)

[9] The district court noted that Bastin disclosed wide ranges of viscosity levels (A72), but those were for the *gelling agent* in its separate layer in Bastin's dual-layer formulation. (A79488 (3:24-35).) Bastin never quantified the viscosity level required of the tampered, dissolved formulation.

therapeutic effect of the active drug. (A6194-95.) It thus deters abusers who attempt to filter as well as those who would attempt to directly syringe the solution, unfiltered. (A6195.) And it specifies the particular viscosity levels that will accomplish such abuse deterrence.

2. The Court Erred In Holding The Claimed Viscosity Levels Obvious

The court nonetheless concluded that the '888 patent's particular quantitative viscosity requirements would have been obvious to one of skill in the art at the time of the inventions. (A84.) Relying on a defense expert, the court found that crafting the first-ever "numerical viscosity requirements" for abuse-deterrent oxycodone "would have involved nothing more than simple experimentation of the syringeability of viscosity standards." (A84.) But in finding it obvious to determine the *optimum* amount of viscosity to impart, the court leapfrogged over the Purdue scientists' significant contribution to the art—first determining that obtaining particular viscosity levels even mattered to deterring abuse, and only then determining what precise viscosity thresholds were optimal. Indeed, in addressing another gelling patent embodied in Reformulated OxyContin®, the same district court recognized that "quantitative measurements of viscosity" would answer "the ultimate question of … whether a gel forms and whether it dissolves," *In re OxyContin Litig.*, 994 F. Supp. 2d 367, 430 (S.D.N.Y.

2014), yet none of the prior art even contemplated quantifying optimal levels of viscosity.

A claim limitation specifying optimal or successful parameters is nonobvious "where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re Kubin*, 561 F.3d at 1359 (quotation marks omitted). That is precisely the case here, especially since the prior art offered no guidance as to which quantitative viscosity levels would deter oxycodone abuse by injection (or snorting). Before it could be obvious to experiment to find an optimal viscosity level, it had to be obvious that imparting particular viscosities—including as high as 60 cP as claimed by claim 7—mattered to abuse deterrence. *See id.*; *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977) (patent's identification of a ratio that optimized the "treatment capacity" of a wastewater treatment device was nonobvious because the asserted prior art was neither directed to, nor suggested performing the inventors' experiments for determining, the optimal value); *see also Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 882 (Fed. Cir. 1998) ("By defining the inventor's problem in terms of its solution, the district court missed [a] necessary antecedent question."). Nothing in the prior art recognized particular viscosity values as relevant to preparing an abuse-deterrent

oxycodone formulation that would deter abuse when moistened with water, but would still maintain a controlled-release matrix with a 12-hour therapeutic effect.

Even where (unlike here) the prior art discloses a value or range of values, a claim to a value that is in close proximity to the prior art is not obvious where "there is no evidence that [the different values] are either not meaningful or one of skill in the art would know to discard the limits set by the prior art." *In re Patel*, 566 F. App'x 1005, 1010 (Fed. Cir. 2014) ("even small differences in formulations can be meaningful"); *cf. Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782-83 (Fed. Cir. 1985) (affirming obviousness where "[t]he proportions" of the prior art and the claims "are so close" that one of ordinary skill "would have expected them to have the same properties"). The prior art here discloses no viscosity levels or ranges at all for a gelling-plus-active-ingredient formulation, let alone any "so close" to the claimed level of "at least about 10 cP" to give an ordinary artisan reason to expect success with that level. The differences between the prior art and claim 7's 60 cP limitation are even greater.

Because the quantitative viscosity levels claimed in the '888 patent were not taught in the prior art, the court legally erred in holding the claims obvious.

C. The Objective Evidence Confirms Nonobviousness

Objective indicia are not only "independent evidence of nonobviousness" but also "may … be the most probative and cogent evidence of nonobviousness in

the record." *InTouch Techs.*, 751 F.3d at 1347. In hindsight, "with the invention fully diagrammed and aided by experts in the field," its advances "in retrospect may seem deceptively simple." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). Objective criteria "inoculate the obviousness analysis against [such] hindsight" by showing the true "contemporaneous attitude toward the asserted invention." *Id.* This Court accordingly requires district courts to consider objective indicia in the obviousness inquiry, and failure to do so requires reversal. *Id.* at 1378-79.

The district court erred as a matter of law in failing to consider important aspects of Purdue's objective evidence of nonobviousness. In addition, on the evidence it did consider, it committed several clear errors.

Commercial, medical, and regulatory success. The '888 patent led Reformulated OxyContin® to unqualified success in the marketplace. Reformulated OxyContin® sales reach about $2 billion annually, an amount directly attributable to its 12-hour therapeutic effect and abuse-deterrent properties, including the '888 patent inventions. The success is all the more remarkable given that, in deterring abuse, Reformulated OxyContin® reduced a portion of its available market share—those abusing the drug in illicit fashion—yet maintained substantially the same level of sales as its predecessor. As real-world epidemiological studies indicated, after Reformulated OxyContin® replaced the

original formulation, abuse declined significantly, especially by injecting and snorting—the routes of abuse addressed by the '888 patent. (A5427-29; A5533-37; A5972-74; A61778-79; A61848.) Also, based on those studies, FDA determined not to approve generics of non-abuse-deterrent original OxyContin® and granted the first-ever abuse-deterrent labeling for an opioid. (A3050-54; A44296-44319; A44490-93; A44732-48; A45120-34.) When FDA explained the basis for those decisions, it explicitly cited Reformulated OxyContin®'s "abuse-deterrent" properties that include "form[ing] a viscous hydrogel [that] cannot be easily prepared for injection." (A44847; *see also* A44842-43.) But for FDA's conclusions, the agency would have approved generic versions of original OxyContin®, which would have substantially eroded sales of the reformulation. (A3322-25; A5540-47.)

At each turn, the court dismissed these multiple objective markers of nonobviousness. The court's own findings demonstrate its error. The court found that "the evidence strongly suggests" Reformulated OxyContin®'s commercial success is "a result of" its efficacy and bioequivalence to the original formulation. (A78.) *Precisely*. The reformulation's achievement was using a gelling agent to deter abuse without disrupting the critical controlled-release profile to provide a 12-hour therapeutic effect like that of the original drug. The court erred as a matter

of law in nonetheless concluding that there was no nexus between the "claimed features" and commercial success. (A78.)

The court's view that Reformulated OxyContin® would not be commercially successful if generic competition with the original formulation were allowed misses the point. (A78-79.) To be sure, that did occur with reformulated Opana® ER, which lost 28 percent of its sales within three months after FDA found Endo's abuse-deterrence claims unsubstantiated and denied Endo's petition to keep generic original Opana® ER off the market. (A5541-42.) That did not occur here specifically because Reformulated OxyContin®'s abuse-deterrent features, including the '888 inventions, convinced FDA to disallow generic versions of original OxyContin® that would have flooded the market.

Finally, with respect to various studies demonstrating Reformulated OxyContin®'s abuse-deterrent features and FDA's reactions to those studies, the court took a too-narrow view of "the relevant criterion." (A77.) It "decline[d] to consider" those studies because "no court has ever deemed 'medical success' to be an objective indication of nonobviousness," and it likewise was "hesitant" to consider evidence of so-called "regulatory success." (A77; A79.) That was legal error. "*[A]ny* secondary considerations" that are relevant to showing the presence of patentable invention must be considered. *KSR*, 550 U.S. at 415; *see also Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699

F.3d 1340, 1349 (Fed. Cir. 2012) ("As we have repeatedly held, 'evidence rising out of the so-called "secondary considerations" must always when present be considered en route to a determination of obviousness.'") (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.3d 1530, 1538 (Fed. Cir. 1983)). And this Court has recognized that "FDA approval … can be relevant in evaluating the objective indicia of nonobviousness" including so-called "commercial success." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (the fact that plaintiff's product was "the first FDA-approved drug to combine vitamin D and corticosteroids into a single formulation for topical application" demonstrated nonobviousness). The court legally erred in dismissing all of this telling evidence of nonobviousness.

Long-felt but unmet need. The court clearly erred in finding that the need for a solution to the oxycodone abuse problem was not "long-felt" on the basis that the "need" only arose in 2001, when Purdue filed its provisional application. (A80-81.) Although opioid abuse surged to a *crisis* at the turn of the century, the testimony cited by the court explained that prescription opioid abuse had been a growing public health concern since the 1990s. (A2882-85; A44724-29.) And when OxyContin® abuse dramatically increased, the need for a solution was urgent. The court clearly erred by demanding a longer research and development period for showing a long-felt but unmet need.

Initial skepticism, unexpected results, and subsequent acclaim. Although Reformulated OxyContin® eventually became the first opioid approved for abuse-deterrent labeling, for years FDA remained skeptical of its effectiveness in that regard. Purdue filed its NDA for Reformulated OxyContin® in 2007, but FDA approved it only in 2010, after requiring Purdue to conduct more comprehensive testing of its abuse-deterrent properties. (A3036-38; A46045-50.) Even after the drug's release, FDA required wide-ranging epidemiological studies to show that the reformulation was a real advance in abuse deterrence. (A3049-52.)

In 2013, the study results met with acclaim. The data indicated that Reformulated OxyContin® reduced abuse and demand on the street. Indeed, the new drug was such an improvement over original OxyContin®—equally therapeutic but with real, meaningful safeguards against abuse—that FDA determined that making the original formulation available was no longer appropriate, and issued its first approval of abuse-deterrent labeling for an opioid (A2896; A3323-26; A4498; A5540-42; A44847-48.) In contrast, Endo failed to convince FDA to grant abuse-deterrent labeling for its Opana® ER product or to prohibit the generic equivalent of its original based on abuse-deterrent properties of the reformulation. (A5540-41.) Also in 2013, the National Association of Attorneys General wrote to FDA, "[app]laud[ing] the development of 'tamper-resistant' drugs and express[ing] hope that '[a]dding the new physical and

chemical features to prescription opioids' would reduce abuse." (A81; A61937-40.) Purdue had done just that with its reformulation.

The court agreed that this abundant evidence showed industry acclaim. (A81.) But because it erred in its assessment of the balance of the objective indicia of nonobviousness, it waved this evidence away as meeting "only one criterion." (A85.) Not only did this reflect the court's error with respect to considering the other factors, but it substantially undervalued this important, objective evidence of acclaim, particularly from the regulatory agency having a deep interest in a solution to the problem and tasked with determining what products may enter or remain in the marketplace, after weighing the benefits of this safety innovation against the prior formulation that lacked this innovative abuse-deterrent characteristic. *See Leo Pharm.*, 726 F.3d at 1358 (FDA approval highlighted key characteristic of patented invention that "prior art formulations did not achieve").

II. CLAIM 7 OF THE '888 PATENT IS NOT INDEFINITE

The district court had no difficulty concluding that all of Amneal's proposed tablets infringed all of the asserted claims—including claim 7, which recites a formulation that contains enough gelling agent to impart a "viscosity of at least about 60 cP" to the tampered-with formulation. (A143 (40:51-52).) Yet the court determined that claim 7, alone, was indefinite because of "the '888 Patent's failure to provide sufficient guidance on shear rate." (A91.) This conclusion was the

product of two legal errors. *First*, the court improperly construed claim 7. An ordinary artisan would evaluate viscosity at shear rates that would most closely resemble the conditions under which an abuser would attempt to draw the substance into a hypodermic needle. *Second*, regardless of construction, the court demanded not *Nautilus*'s "reasonable certainty," but something more akin to absolute or metaphysical certainty. Claim 7—like the other claims—"inform[s] those skilled in the art about the scope of the invention with reasonable certainty." *See Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014).

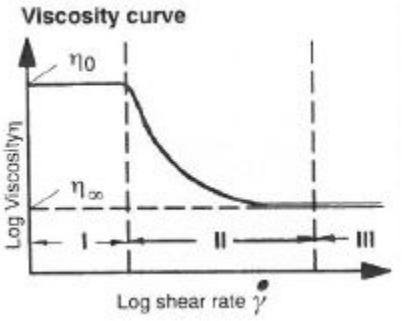
A. One Skilled In The Art Would Know To Measure Viscosity In The Zero-Shear Region

Claim construction proceeds primarily from the intrinsic evidence, and the specification is "[u]sually … dispositive; it is the single best guide to the meaning of" the claims. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc). Extrinsic evidence can be useful, but only where it is not employed to contradict the intrinsic record. *Id.* at 1317; *Kaneka Corp. v. Xiamen Kingdomway Grp. Co.*, 790 F.3d 1298, 1304 (Fed. Cir. 2015).

The intrinsic and extrinsic record consistently guides one of ordinary skill to utilize the zero-shear range when testing viscosity in the context of the '888 patent.

1. The Intrinsic And Extrinsic Evidence Supports Purdue's Construction

There is no question, as the district court noted, that "[t]he dosage forms contemplated by the '888 Patent are pseudo-plastic, non-Newtonian solutions, which means that their viscosity depends to some degree on shear rate." (A45.) The Schramm textbook (A61918-29), reproduced in the district court's opinion (A46) and above, shows the typical viscosity curve of pseudo-plastic materials:



Schramm also shows (and experts in this case confirm) that one of ordinary skill knew that pseudo-plastic materials would have viscosity that varies with shear rates in region II, but in the "zero shear" region with "very low" shear rates (region I), viscosity is constant and will approximate the material's viscosity at rest. (A61924-25; A45-46; A5616-20; A6184-85; A6279.) As this Court has explained, a patent "need not include in the specification that which is already known to and available to a person of ordinary skill in the art." *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1368 (Fed. Cir. 2011).

With this knowledge, the ordinarily skilled artisan would find in the '888 patent clear (and, perforce, "reasonably certain") guidance on which range of shear rates to use: The artisan would pick the zero-shear region because it most closely resembles the state of the material when abused, *i.e.*, when an abuser attempts to pull the tampered, dissolved drug into a needle (or when the substance rests in the abuser's nasal cavity). (A45-46; A5616-20; A6184-85; A6279.) Why is this so? Because the '888 inventions deter abuse by making the tampered-with oxycodone formulation "difficult[]" to pull through a needle and thus "unsuitable for injection" (or, in the case of intranasal abuse, "stick to the nasal passage and minimize absorption of the abusable substance"). (A125 (3:5-36); A50.) As a matter of common sense, which the ordinary patent-reading artisan possesses, *see KSR*, 550 U.S. at 420, potential abusers do not attempt to pull dissolved, aqueous, drug-containing solutions into a needle from a spinning centrifuge. Rather, they pull solutions from non-moving spoons, vials, cups, etc. (and when a crushed tablet is snorted and gels, the material is similarly static, stuck in the abuser's nose). (A6185; A6279.) *See Howmedica v. Osteonics Corp. v. Tranquil Prospects, Ltd.*, 401 F.3d 1367, 1371-72 (Fed. Cir. 2005) (choosing a particular construction because one of ordinary skill in the art would "readily ascertain" that construction based on the "overriding purpose of the invention" as disclosed in the written description).

Common sense therefore would compel the ordinary artisan reading the '888 patent to test viscosity in the zero-shear region. The court correctly rejected Amneal's attempt to sow ambiguity into the viscosity test based on the patent's silence with respect to other viscosity-testing parameters such as temperature; the court recognized that "common sense" would dictate testing at temperatures approximating those at which an abuser would abuse the drug. (A50-51 ("An ordinary skilled artisan would understand as a matter of common sense, however, that abusers do not inject, snort, or swallow extremely hot liquids."); A52 n.8 (noting "the common sense conclusion that abusers do not administer boiling solutions").) Yet when it came to shear rate, "common sense" took a holiday.

Other aspects of the '888 patent confirm that testing conditions should resemble the conditions of abuse. Example 3 describes how the inventors themselves recreated a common abuse scenario—crushing and moistening an oxycodone tablet, then trying to pull it through an insulin syringe—to test just how viscous they needed to make the formulation to deter abuse by injection. (A139 (Example 3).) With this disclosure, the patent makes clear that the viscosity that matters is the viscosity of the dosage form after it has been "tamper[ed] by dissolution" and is in a static state, *i.e.*, about to be pulled into a needle (or resting in the moist nasal cavity). *See Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1076-77 (Fed. Cir. 2005) (where the specification explains that the inventors

undertook a particular type of test to "confirm" that a product met a quantitative claim limitation, and provided the results in a figure, that is an "unmistakabl[e] instruct[ion]" to one skilled in the art to use that test); *Kinetic Concepts, Inc. v. Blue Sky Med. Grp., Inc.*, 554 F.3d 1010, 1022 (Fed. Cir. 2009) (construing a claim limitation requiring "at least 50%" reduction in bacterial density to require measurement using a particular method on the basis that "a person of ordinary skill in the art would know which method to use because Example 2 of the … patent describes a particular method"); *Chimie v. PPG Indus. Inc.*, 402 F.3d 1371, 1378-80 (Fed. Cir. 2005) (concluding that, although there were other means for assessing "dustiness," "the only articulation of the dustiness of the claimed invention" was in an example in the specification, and thus the term "dust-free and non-dusting" was construed in light of that example).

2. The District Court Improperly Dismissed The Evidence Supporting Purdue's Construction

The district court was correct to recognize that, as a starting point, the skilled artisan would use shear rates within a range from .01 to 100 reciprocal seconds. (A5615-17; A6183.) But the court then veered off the artisan's path. Where the artisan would have tested within that range to find the zero-shear region, the court instead demanded that the '888 patent precisely define a specific range of shear rates, even though the claims cover various dosage forms each having Schramm's classic curve shape but with boundaries that could differ for each region. (A48;

A6183-84.) By making this demand, the court failed to honor *Nautilus*'s "reasonable certainty" standard, and instead injected unreasonable ambiguity into a claim that had none.

The court improperly dismissed the full weight of the intrinsic evidence guiding one of skill in the art to locate the zero-shear region. The court did so based solely on its view that Example 3 was only "a single example" supporting Purdue's construction. (A46.) As explained above, the patent in its entirety—not just Example 3—gave one of ordinary skill in the art all the guidance needed to determine viscosity: Test under conditions most closely resembling the conditions of abuse. Although the court stated that it had "heard no evidence" that injection or snorting gelled material "necessarily require solutions at rest" (A47), the patent specification, expert testimony on how one skilled in the art would read the patent, and common sense expressly refute this. (A139 (Example 3); A6185; A6279.)[10]

In any event, a "single example" is enough. As this Court has held, a single example disclosing a particular measurement method is sufficient to construe a quantitative claim limitation to require measurement by that method. *See Blue Sky*

[10] The court also faulted Purdue for not presenting evidence that oral ingestion also required solutions at rest. (A46-47.) The '888 inventions, however, are directed to abuse not by oral ingestion, but by "injection and/or inhalation." (A49249 (3:9); A108447 (explaining that the patent is directed to "parenteral abuse," including abuse by injection).)

Med., 554 F.3d at 1022; *Chimie*, 402 F.3d at 1378-80. Here, Example 3 and its focus on viscosity when the formulation is being pulled into a syringe demonstrates with clarity that the viscosity that matters is its viscosity at rest, *i.e.*, viscosity tested in the material's zero-shear region.

The court also erred in its evaluation of the extrinsic evidence. The court found that the extrinsic evidence showed that "specifying shear rate is standard practice among ordinarily skilled artisans." (A87.) But the practice of disclosing fixed shear rates was far from "standard." A defense expert saw no need to record shear rate. (A6141; *see also* A108853-55 (chart specifying viscosities of particular materials without specifying shear rate).) The court's evidence—an instrument manual, a brochure for PEO, and two patents—did not demonstrate that this was standard practice, either. None of that evidence actually stated a shear rate; it merely indicated which spindle to use and gave either a "test speed" or "rotational speed" or "rpm" (A49233 (6:2-9); A83988 (3:14-23); A108840), or, in the case of one instrument manual, indicated that one should "control or specify" shear rate (A109002-03).

More important, though: Whether or not specifying shear rate for viscosity testing is "standard practice" as a general matter, the '888 patent was plenty clear on the conditions for testing, and extrinsic evidence should not be used as a tool for *introducing* uncertainty into the claims. *See Kaneka*, 790 F.3d at 1304. One

skilled in the art would not be stymied by the absence of any explicit specification of shear rate in the claims or specification here; the specification's repeated emphasis on deterring common, described abuse scenarios would lead one skilled in the art to select the comparable zero-shear region as the appropriate range for viscosity testing.

Finally, the court clearly erred in dismissing the Schramm textbook's support for Purdue's construction. The court pointed out that Schramm does not name zero shear as the "default" or "definitive" shear rate for testing the viscosity of pseudo-plastic liquids, and noted that region III is also "identifie[d] by a term of art." (A47-48.) The court missed the point: Schramm labels both region I and region III as "Newtonian range[s]" because "even the viscosity of non-Newtonian liquids is independent of shear rate" in those regions. But Schramm's identification of region I as "zero shear viscosity," and its detailed explanation of that term, demonstrates that, *in the context of the '888 patent*, one of ordinary skill in the art would in fact look to region I, not the high rates in regions II or III that do not approximate a material's static state. *See Teva*, 135 S. Ct. at 733 (courts undertake "a legal analysis" to determine "whether a skilled artisan would ascribe that same meaning to that term *in the context of the specific patent claim under review*" (emphasis in original)). OxyContin® abusers are not pulling tablets out of fast spinning centrifuges right before injecting or snorting.

* * * *

Under the proper construction, there is no doubt that Amneal infringes. In fact, Amneal has never argued that infringement of its accused tablets (or Teva's) depends on which shear rate *within* the zero-shear region is chosen, and for good reason: It is undisputed that a pseudo-plastic dosage form's viscosity remains constant throughout the zero-shear region. (A61-66; A5616-17; A5624-25; A6183-86; A61924.)

And since, under this proper construction, infringement of claim 7 would not depend on which shear rate within the zero-shear region is chosen, the claim is not indefinite. (A5624 (Teva's 30 mg tablet remained "above the 60 centipoise line in the region of the zero shear viscosity.").) After all, as a decision quoted by the Supreme Court in *Nautilus* explains, the definiteness requirement aims to avoid a "zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims." *United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942) (cited in *Nautilus*, 134 S. Ct. at 2129). The evaluation of infringement here was not uncertain; even the court, which thought the claims indefinite, had no difficulty finding infringement. The court's contrary indefiniteness determination, based on its erroneous claim construction, should be reversed.

B. Even Under The Court's Construction, Claim 7 Is Not Indefinite

Even if the court were correct in construing the claim to permit testing across, "at a minimum," shear rates between .01 and 100 reciprocal seconds (A91), the skilled artisan could still determine with "reasonable certainty" whether a product meets claim 7 as construed—just as the court was able to adjudicate Amneal's infringement without difficulty. "Reasonable certainty" is not "metaphysical" or "absolute" certainty. *See Nautilus*, 134 S. Ct. at 2128; *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1380 (Fed. Cir. 2001) (in light of the "statutory presumption of validity," "close questions of indefiniteness in litigation involving issued patents are properly resolved in favor of the patentee"); *see also* 35 U.S.C. § 112(b). All experts used shear rates between .01 to 100 reciprocal seconds; none used rates any higher. And using that range, the court was able to determine that all of Amneal's tablets infringe across that entire range of shear rates. (A61-66; A5693-94; A5863-64; A61409-15.)

Even if there were some theoretical uncertainty at the margins, the facts of this case would not support finding any claim indefinite. In the wide range chosen by the court, all of Amneal's tablets exceeded 60 cP. (A63-64; A5625-26; A61409-15.) So did Teva's. (A5623-24; A61491-97.) To the extent there is a question of fact as to whether Teva's 30 mg tablet meets the 60 cP viscosity limitation based on those test results, that is a question of infringement, not

indefiniteness—and indeed not at issue in this case because Teva is no longer a defendant.

Given the reasonable certainty of the claims even under the court's construction, the indefiniteness ruling should be reversed.

CONCLUSION

The judgment of invalidity should be reversed.

Respectfully submitted,

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ADDENDUM

In re: OXYCONTIN ANTITRUST LITIGATION	04 Md. 1603 (SHS)
PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., and PURDUE PHARMACEUTICALS L.P., Plaintiffs, -against- AMNEAL PHARMACEUTICALS, LLC, Defendant.	13 Civ. 3372 (SHS)
PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., PURDUE PHARMACEUTICALS L.P., and GRÜNENTHAL GMBH, Plaintiffs, -against- TEVA PHARMACEUTICALS USA, INC., Defendant.	13 Civ. 4606 (SHS) OPINION & ORDER

SIDNEY H. STEIN, U.S. District Judge.

This Hatch-Waxman Act litigation is the latest in a series of related actions concerning the brand-name drug OxyContin, which is manufactured and sold by plaintiffs Purdue Pharma L.P., The P.F. Laboratories, Inc., and Purdue Pharmaceuticals L.P. (collectively, "Purdue"). Defendants—Amneal Pharmaceuticals, LLC and Teva Pharmaceuticals USA, Inc.—have filed Abbreviated New Drug Applications ("ANDAs") seeking to sell generic versions of OxyContin. Plaintiffs contend that defendants' ANDAs infringe two patents that claim the OxyContin formulation currently sold in the United States. Purdue, as well as plaintiff Grünenthal GmbH (collectively with Purdue, "plaintiffs"), developed these patents to address the problem of widespread abuse of original OxyContin by users who snorted or injected crushed or dissolved

tablets.[1] These patents, along with others the Court has previously considered, are embodied in Purdue's "Reformulated OxyContin," the only form of the drug that Purdue now sells in the United States.

The two patents before the Court are Purdue's U.S. Patent No. 8,337,888 ("'888 Patent") (Ex. 1 to Decl. of Rebecca R. Hermes dated Jan. 15, 2014 ("Hermes Decl.")) and Grünenthal's U.S. Patent No. 8,309,060 ("'060 Patent") (Ex. 2 to Hermes Decl.). On March 7, 2014, the Court held a *Markman* hearing to construe the disputed portions of the claims at issue in these two patents. This Opinion and Order is the result.

I. BACKGROUND

The Court assumes familiarity with Purdue's development of Reformulated OxyContin, as detailed in the Court's August 23, 2013 Claim Construction Opinion and Order, 965 F. Supp. 2d 420 (S.D.N.Y. 2013), and its January 14, 2014 Findings of Fact and Conclusions of Law, No. 04 Md. 1603, 2014 WL 128013 (S.D.N.Y. Jan. 14, 2014).

The '888 Patent is a product of inventions Purdue made in the early 2000s. *See* '888 Patent at [60], [63] (listing related application data); (Pls.' Opening Br. 1.) After reports of abuse of original OxyContin emerged, scientists at Purdue began exploring how to deter snorting and injection, the most common methods of abuse. (Pls.' Opening Br. 6; Ex. 3 to Hermes Decl., at 24, 111; Ex. 4 to Hermes Decl., at 24–25). The '888 Patent discloses and claims a dosage form that utilizes a gelling agent to deter abuse by snorting and injection. '888 Patent at 2:64–3:24, 7:4–12, 40:25–29. The patent claims polyethylene oxide ("PEO") as an acceptable gelling agent. *Id.* at 40:25. Purdue scientists determined that when a dosage form containing the gelling agent was combined with a small quantity of aqueous liquid, the mixture formed a gel that was difficult to inject from a syringe. *Id.* at 3:5–19. Moreover, when the dosage form was crushed and then snorted, it became gel-like through contact with moisture in the nasal passages, reducing the amount of the drug that could be absorbed nasally. *Id.* at 3:25–30. The '888 Patent issued in December 2012. *Id.* at [45].

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[1] Crushing the tablet defeats its controlled-release mechanism. '888 Patent at 1:26–29. In addition, parenteral (non-oral) administration typically results in greater potency than oral administration. *Id.* at 1:18–20. OxyContin abusers achieved a "high" by crushing the tablets and then injecting or snorting the powder. *See id.* at 1:20–25, 7:4–12.

The '060 Patent is a divisional application of the application that issued as Grünenthal's U.S. Patent No. 8,114,383 ("the '383 Patent").[2] '060 Patent at [62]. Like the '383 patent, the '060 Patent discloses and claims "a thermoformed dosage form" that resists crushing by virtue of its 500 Newton breaking strength. *Compare* '060 Patent at 2:17–32, 21:13–14, *with* '383 Patent at 2:7–13, 21:1–14. The '060 Patent names several polymers, including PEO, as suitable hardening agents. '060 Patent at 5:54–63. Unlike the '383 Patent, however, the '060 Patent includes claims that call for additional protection against abuse should an abuser nonetheless manage to crush the dosage form. *Id.* at 6:24–34, 21:37–51. This further protection is achieved through the addition of irritants, bittering agents, dyes, emetics, and/or gelling agents to the dosage form, which make inappropriate administration of the drug difficult or unpleasant. *Id.* at 6:24–34, 8:28–38, 12:1–7, 21:37–51.

II. LEGAL STANDARD

"[T]he claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks and citations omitted). "Generally, a claim term is given the ordinary and customary meaning as understood by a person of ordinary skill in the art at the time of invention." *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, No. 2013-1201, 2014 WL 1855416, at *8 (Fed. Cir. May 9, 2014).

The Federal Circuit has stressed "the importance of intrinsic evidence" in discerning the ordinary and customary meaning of claims. *Phillips*, 415 F.3d at 1317. The analysis "must begin and remain centered on the claim language itself." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004) (internal quotation marks and alterations omitted). "Claims, however, must be construed in light of the appropriate context in which the claim term is used." *Aventis Pharm. Inc. v. Amino Chems. Ltd.*, 715 F.3d 1363, 1373 (Fed. Cir. 2013). That context includes the specification, which "is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (internal

[2] The Court found the '383 Patent invalid as anticipated and obvious in its January 2014 Findings of Fact and Conclusions of Law. *In re OxyContin Antitrust Litig.*, 2014 WL 128013 at *86, *90.

quotation marks and citation omitted). "The prosecution history too, as part of the intrinsic record, has an important role in claim construction by supplying context to the claim language." *Aventis*, 715 F.3d at 1373.

Courts may also look to extrinsic evidence—"all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317 (internal quotation marks and citations omitted). Such evidence, however, may not be used "to contradict claim meaning that is unambiguous in light of the intrinsic evidence." *Id.* at 1324. "Ultimately, the construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Takeda Pharm. Co. Ltd. v. Zydus Pharm. USA, Inc.*, 743 F.3d 1359, 1363 (Fed. Cir. 2014) (internal quotation marks, citations, and alterations omitted).

With these legal principles in mind, the Court addresses the disputed claims.

III. Construction of the Disputed Claims in the '888 Patent

Of the '888 Patent's 24 claims, Purdue asserts all but claim 10 against defendants.[3] (Pls.' Opening Br. 10.) The parties dispute the meaning of certain terms in independent claim 1 and dependent claims 23 and 24. The disputed claims read:

> 1. A controlled release oral dosage form comprising:
>
> . . .
>
> a gelling agent comprising polyethylene oxide in an effective amount to impart a viscosity of at least about 10 cP when the dosage form is subjected to tampering by dissolution in from about 0.5 to about 10 ml of an aqueous liquid;
>
> . . .
>
> 23. The controlled release oral dosage form of any of claims 2, 4, 5, 6 and 7, wherein the viscosity is obtained when the dosage form is subjected to tampering by crushing and dissolution in the aqueous liquid.
>
> 24. The controlled release oral dosage form of any of claims 2, 4, 5, 6 and 7, wherein the viscosity is obtained when the dosage form is

[3] Purdue asserts claims 8 and 9 against Teva alone. (Pls.' Opening Br. 10 n.6.)

subjected to tampering by dissolution in the aqueous liquid with heating greater than 45° C.

'888 Patent at 40:22, 40:25–29, 42:10–17. The Court separately addresses each of the disputed terms below.

A. Claim 1

Claim 1 provides that the dosage form obtains "a viscosity of at least about 10 cP when [it] is subjected to tampering by dissolution in from about 0.5 to about 10 ml of an aqueous liquid." '888 Patent at 40:26–29. The parties refer to this claim language as the "viscosity test." (Hr'g Tr. 51, 54.) Purdue submits only the term "tampering" for construction, urging the Court to give it the same meaning as "tampered dosage form," which the patentees defined in the patent specification at 4:15–25. (Pls.' Opening Br. 11.) Defendants specifically "do not separately address this term" and decline to propose a construction. (Defs.' Opening Br. 7 n.6.) They instead submit the viscosity test in its entirety for the Court's consideration. They do not suggest a particular construction, however, arguing that the viscosity test is indefinite. (Defs.' Opening Br. 7 & n.6, 8.)

1. The Court declines to rule on the issue of indefiniteness of the viscosity test prior to trial

Defendants admit that the specification provides a definition of "tampering" (through its definition of "tampered dosage form"), but argue that the viscosity test of claim 1 is indefinite when read in its entirety. (Hr'g Tr. 53–54, 62; Defs.' Opening Br. 7–8). Defendants contend that the patent provides no guidance on the various factors that they argue impact viscosity, viz., the particle size of the dosage form; the type of aqueous liquid in which it is dissolved; how long it remains in the aqueous liquid; whether the dosage form and aqueous liquid are stirred; and the temperature, shear rate, and type of equipment used to measure viscosity. (Defs.' Opening Br. 8–13; Hr'g Tr. 54–56, 63–64.)

The Court refrains from ruling on the issue of indefiniteness prior to trial. A full record will better enable the Court to determine whether the various factors that defendants have identified render the viscosity test insolubly ambiguous. *See In re OxyContin Antitrust Litig.*, 965 F. Supp. 2d 420, 432 n.3 (S.D.N.Y. 2013); *Alcon Research, Ltd. v. Barr Labs. Inc.*, No. 09-CV-0318, 2011 WL 3901878, at *16 (D. Del. Sept. 6, 2011) ("We find that the

indefiniteness issue is best decided at trial and defer consideration on it until that time."). The Court therefore proceeds to construe the disputed claim language.

2. ***"Tampering by dissolution" means dissolution of the dosage form that is optionally accompanied by additional means of tampering***

As noted above, Purdue submits the term "tampering" for construction, asking the Court to construe it the same way the patentees defined "tampered dosage form." (Pls.' Opening Br. 11; Hr'g Tr. 47.) Purdue overlooks the fact that claim 1 does not utilize the solitary term "tampering," but rather refers to "tampering by dissolution." '888 Patent at 40:27–28. Simply adopting the patentees' definition of "tampered dosage form," therefore, would not resolve the issues of construction that claim 1 presents.

Still, the specification's definition of "tampered dosage form" sheds light on the meaning of "tampering by dissolution." It provides:

> The term "tampered dosage form" is defined for purposes of the present invention to mean that the dosage form has been manipulated by mechanical, thermal, and/or chemical means which changes the physical properties of the dosage form, e.g., to liberate the opioid agonist for immediate release if it is in sustained release form, or to make the opioid agonist available for inappropriate use such as administration by an alternate route, e.g., parenterally. The tampering can be, e.g., by means of crushing, shearing, grinding, chewing, dissolution in a solvent, heating, (e.g., greater than about 45° C.), or any combination thereof.

'888 Patent at 4:15–25. Defendants agree that this language explains what the patentees meant by tampering. (Hr'g Tr. 54, 62.) The issue then becomes how to construe the term "tampering by dissolution" that is found in claim 1.

Importantly, no party argues that "tampering by dissolution" means tampering *only* by dissolution, to the exclusion of other means of tampering described in the specification. (*See* Pls.' Opening Br. 12; Defs.' Opening Br. 8; Decl. of Fernando J. Muzzio dated Jan. 15, 2014 ("Muzzio Decl.") ¶ 30.) Both parties' expert witnesses noted that a person of

ordinary skill in the art understands that additional manipulation of the dosage form during or prior to dissolution—such as by heating, crushing, or grinding—tends to facilitate the process of dissolution. (Decl. of Martyn C. Davies dated Feb. 14, 2014 ("Davies Decl.") ¶ 39; *see* Muzzio Decl. ¶ 32.)

Moreover, the specification clarifies that although claim 1 specifically requires dissolution, other forms of tampering may also occur. The specification twice refers to a dosage form that is "tampered with" and then dissolved. '888 Patent at 7:21–24, 7:28–31. It further provides:

> In certain preferred embodiments, when the dosage form is tampered with and exposed to a small amount (e.g., less than about 10 ml) of an aqueous liquid (e.g., water), the dosage form will be unsuitable for injection and/or inhalation. Upon the addition of the aqueous liquid, the tampered dosage form preferably becomes thick and viscous, rendering it unsuitable for injection.

'888 Patent at 3:5–11. By disclosing a preferred embodiment calling for tampering *followed by* exposure to an aqueous liquid, the patentees signaled that the phrase "tampering by dissolution" encompasses more than just dissolution. Indeed, if claim 1—from which all the other claims depend—were read to exclude other forms of tampering, the preferred embodiment would not fall within the patent. Such constructions are strongly disfavored and require "highly persuasive evidentiary support," which the '888 specification lacks. *SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1378–79 (Fed. Cir. 2013) (internal quotation marks and citation omitted).

For these reasons, the Court construes "tampering by dissolution" to mean dissolution of the dosage form that is optionally accompanied by the methods of tampering described in the specification's definition of "tampered dosage form."

3. "Aqueous liquid" means "aqueous liquid"

Purdue urges the Court to specifically identify water as an example of the "aqueous liquid" referenced in the viscosity test. (Pls.' Opening Br. 13 (proposing the language "e.g., water").) The parties agree that water is an example of an aqueous liquid and that the term "aqueous liquid" in claim 1 is not limited to water. (Hr'g Tr. 49, 54.) Nor is it disputed that a person of ordinary skill in the art would understand that water is an example of

an aqueous liquid. (Muzzio Decl. ¶ 33; Davies Decl. ¶ 43.) Consequently, Purdue's proposed clarification of "aqueous liquid" is unnecessary because there is no actual dispute over that term. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (stating that "only those terms need be construed that are in controversy").

* * *

For these reasons, the Court construes claim 1 of the '888 Patent to read as follows:

> 1. A controlled release oral dosage form comprising:
>
> . . .
>
> a gelling agent comprising polyethylene oxide in an effective amount to impart a viscosity of at least about 10 cP when the dosage form is subjected to tampering by dissolution in from about 0.5 to about 10 ml of an aqueous liquid; such dissolution having optionally been accompanied by tampering with the dosage form through mechanical, thermal, and/or chemical means of manipulation which changes the physical properties of the dosage form, e.g., to liberate the opioid agonist for immediate release if it is in sustained release form, or to make the opioid agonist available for inappropriate use such as administration by an alternate route, e.g. parenterally; the tampering can be, e.g., by means of crushing, shearing, grinding, chewing, dissolution in a solvent, heating (e.g., greater than about 45° C.), or any combination thereof;
>
> . . .

B. Claims 23 and 24

Due to their similarity, the Court addresses claims 23 and 24 together. Both claims recite a "dosage form of any of claims 2, 4, 5, 6, and 7." '888 Patent at 42:10–11, 42:14–15. Claims 23 and 24 exhibit a "multiple dependent claim" structure—they "refer[] back in the alternative to more than one preceding independent or dependent claim." MPEP § 608.01(n) (9th ed., Mar. 2014). Claims 2, 4, 5, 6, and 7, in turn, depend from claim 1. '888 Patent at 40:33, 40:41, 40:45, 40:47, 40:51. Therefore, claims 23 and 24 contain all the limitations of claim 1, as well as any further limitations imposed by whichever of claims 2, 4, 5, 6, or 7 is being considered. *See* 35 U.S.C. § 112(e) ("A multiple dependent claim shall be construed to

incorporate by reference all the limitations of the particular claim in relation to which it is being considered.").

Claims 23 and 24, as the parties agree, limit the claims from which they depend by prescribing a specific method of tampering. (*See* Pls.' Opening Br. 14–15; Defs.' Opening Br. 14.) Claim 23 provides that "the viscosity is obtained when the dosage form is subjected to tampering by crushing and dissolution in the aqueous liquid." '888 Patent at 42:11–13. Similarly, claim 24 states that "the viscosity is obtained when the dosage form is subjected to tampering by dissolution in the aqueous liquid with heating greater than 45° C." *Id.* at 42:15–17.

Defendants argue that claims 23 and 24 are indefinite for the same reason as claim 1: their lack of guidance on the variables that, according to defendants, influence viscosity. (Defs.' Opening Br. 14.) However, defendants propose no construction for the Court to consider. Again, the Court defers ruling on the issue of indefiniteness.

With respect to claim 23, Purdue asks the Court to construe the disputed language to mean "wherein the viscosity of at least about 10 cP is obtained when the dosage form is subjected to manipulation by tampering that includes crushing and dissolution in from about 0.5 to about 10 ml of an aqueous liquid, e.g. water." (Pls.' Opening Br. 14.) Its proposed construction of claim 24 is very similar: "wherein the viscosity of at least about 10 cP is obtained when the dosage form is subjected to manipulation by tampering that includes dissolution in from about 0.5 to about 10 ml of an aqueous liquid, e.g. water, with heating greater than 45° C." (*Id.* 15.) In essence, Purdue attempts to clarify the required level of viscosity and amount of aqueous liquid by referring back to the language of claim 1, from which claims 23 and 24 (by way of claims 2, 4, 5, 6, and 7) depend.

The Court rejects Purdue's constructions because they create the potential for misinterpretation of the claim language. Were the Court to adopt Purdue's proposed language, claims 23 and 24 would appear to disregard the limitations of claims 6 and 7. *See* 35 U.S.C. § 112(e); *Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 806 (Fed. Cir. 2007) (noting that "independent claims are presumed to have broader scope than their dependents"); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 1000 (Fed. Cir. 1995) (en banc) (noting that "a dependent claim includes all of the limitations of the independent claim"), *aff'd*, 517 U.S. 370 (1996). Specifically, claim 6 provides that the dosage form is dissolved in about 1

to about 3 ml of an aqueous liquid, '888 Patent at 40:48–50, a range of volume that is more limited than Purdue's suggested construction. Similarly, claim 7 requires a viscosity of "at least about 60 cP," *id.* at 40:52, six times greater than Purdue's suggestion of 10 cP. Although the presumption that dependent claims are narrower than the claims from which they depend is not irrefutable, *see Acumed*, 483 F.3d at 806, there is no evidence to suggest that the patentees disavowed that general rule. Consequently, even if adopting Purdue's constructions would not technically override the limitations of claims 6 and 7, it would create unnecessary confusion because Purdue's proposed viscosity and volume limitations are meaningless when read in light of the dissimilar requirements of claims 6 and 7.

To avoid the problems posed by Purdue's constructions, the Court will construe claims 23 and 24 to refer to the "requisite viscosity" and the "specified volume of aqueous liquid," rather than utilizing the particular ranges of viscosity and volume that Purdue suggests. Because claims 23 and 24 do not specify the necessary viscosity and volume of aqueous liquid but do refer back to other claims, a person of ordinary skill in the art would know to look to those claims to ascertain that information. (*See* Davies Decl. ¶ 44.) In other words, a person of skill in the art would interpret claims 23 and 24 to require about 0.5 to about 10 ml of aqueous liquid and a viscosity of at least about 10 cP, if they depend from claims 2, 4, or 5; about 1 to about 3 ml of aqueous liquid and viscosity of at least about 10 cP, if they depend from claim 6; and about 0.5 to about 10 ml of aqueous liquid and a viscosity of at least about 60 cP, if they depend from claim 7.

The Court does agree with Purdue, however, that claims 23 and 24 should be construed to allow methods of tampering besides those specified in the claims. (*See* Pls.' Opening Br. 14–15.) Defendants do not argue to the contrary. The specification does not shed much light on the meaning of claims 23 and 24. Both claims require dissolution, however, and a person of ordinary skill in the art understands that the methods of tampering described in the specification tend to facilitate dissolution. (Davies Decl. ¶ 39; *see* Muzzio Decl. ¶ 32.) Moreover, the claims' internal structure and use of the phrase "tampering by" are very similar to claim 1. Because there is no evidence that the patentees sought to limit claims 23 and 24 to the specified means of tampering, the Court will give them the broader interpretation that is consistent with its construction of claim 1. *Cf.*

Am. Piledriving Equip., Inc. v. Geoquip, Inc., 637 F.3d 1324, 1333 (Fed. Cir. 2011) ("Where a claim term is used consistently throughout the claims, the usage of the term in one claim can often illuminate the meaning of the same term in other claims.") (internal quotation marks, citation, and alterations omitted). The Court therefore construes claims 23 and 24 to require "tampering that includes"—but is not limited to—the particular methods specified in those claims.

Finally, the Court rejects Purdue's request to specify water as an example of an aqueous liquid. As with claim 1, that construction is unnecessary.

* * *

For these reasons, the Court construes claims 23 and 24 of the '888 Patent to read as follows:

> 23. The controlled release oral dosage form of any of claims 2, 4, 5, 6 and 7, wherein the requisite viscosity is obtained when the dosage form is subjected to tampering that includes crushing and dissolution in the specified volume of aqueous liquid.
>
> 24. The controlled release oral dosage form of any of claims 2, 4, 5, 6 and 7, wherein the requisite viscosity is obtained when the dosage form is subjected to tampering that includes dissolution in the specified volume of aqueous liquid with heating greater than 45° C.

IV. CONSTRUCTION OF THE DISPUTED CLAIMS IN THE '060 PATENT

Plaintiffs allege that Teva's[4] ANDA infringes 17 of the '060 Patent's 34 claims: 2, 4, 5, 8, 9, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, and 34. (Pls.' Opening Br. 19.) Of these, the parties only dispute the meaning of certain terms in dependent claim 9, which must be read in conjunction with independent claim 1. Independent claim 1 reads as follows:

> 1. An abuse-proofed, thermoformed dosage form comprising one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C), wherein the polymer (C) has a molecular weight of at least 0.5 million according to rheological

[4] Plaintiffs do not assert the '060 Patent against defendant Amneal.

measurements, and optionally at least one wax (D), wherein the dosage form exhibits a breaking strength of at least 500 N.

'060 Patent at 21:6–14. Dependent claim 9 claims, in pertinent part:

> 9. A dosage form according to claim 1, which additionally comprises at least one of the following components a)-f):
>
> . . .
>
> (b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel optionally remains visually distinguishable when introduced into a further quantity of an aqueous liquid,
>
> . . .

Id. at 21:37–38, 21:41–46. The parties dispute the meaning of four terms in claim 9, each of which the Court addresses below.

A. Construction of "viscosity-increasing agent (b)"

The bulk of the parties' dispute centers on the meaning of the following phrase in claim 9: "A dosage form according to claim 1, which additionally comprises . . . at least one viscosity-increasing agent." '060 Patent at 21:37–41. Specifically, the parties disagree whether viscosity-increasing agent (b), which is recited in claim 9, must be a different substance than hardening polymer (C), which imparts the breaking strength of 500 Newtons required by claim 1. *See* '060 Patent at 5:54–58, 21:6–14, 21:41. Plaintiffs contend that a single substance may serve both functions, so long as it confers the requisite characteristics of both hardness and viscosity. (Pls.' Opening Br. 22, 24.) Teva argues that hardening polymer (C) and viscosity-increasing agent (b) must be two separate and distinct substances; they further allege that the latter is limited to a particular list of substances contained in the specification. (Defs.' Opening Br. 16–19.)

1. Viscosity-increasing agent (b) and hardening polymer (C) must be different components

The Court begins with the language of claims 1 and 9. *See Innova/Pure Water, Inc.*, 381 F.3d at 1116. Claim 1 sets out a list of four elements that the dosage form comprises: one or more active ingredients with abuse

potential (A), optional auxiliary substances (B), at least one synthetic or natural polymer (C), and optionally at least one wax (D). '060 Patent at 21:6–14. Claim 9 then specifies several components, including viscosity-increasing agent (b), that the dosage form may "additionally comprise[]" as optional auxiliary substances (B). *Id.* at 6:35–40 (defining components a)-f) as auxiliary substances (B)), 21:37-51.

At the *Markman* hearing, the parties agreed that "additionally comprises" is not a term of art, and that a person of ordinary skill in the art would not construe the term differently from a lay person. (Hr'g Tr. 10, 20.) The Court agrees with Teva that the most natural reading of the phrase "additionally comprises" would require *something other* than hardening polymer (C). *See Phillips*, 415 F.3d at 1314 ("In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words."). Moreover, the fact that claim 1 lists hardening polymer (C) and auxiliary substances (B) as separate elements indicates that viscosity-increasing agent (b) cannot be the same substance as polymer (C). *See Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1254 (Fed. Cir. 2010) ("Where a claim lists elements separately, the clear implication of the claim language is that those elements are distinct components of the patented invention.") (internal quotation marks, citations, and alterations omitted). The structure of the claim language itself, then, indicates that two different substances must serve as hardening polymer (C) and viscosity-increasing agent (b).

The specification provides additional support for this construction. The following passages are probative:

- "Another option for preventing abuse of the dosage form according to the invention consists in adding at least one viscosity-increasing agent as a further abuse-preventing component (b) to the dosage form . . . ." '060 Patent at 8:19–22.
- "If component (b) is added to the dosage form according to the invention, one or more viscosity-increasing agents are used . . . ." *Id.* at 8:63–65.
- "[T]he dosage forms according to the invention may, in a preferred embodiment, contain further agents which complicate or prevent abuse as auxiliary substances (B)." *Id.* at 6:31–34.

"[C]ontain further agents," "adding at least one viscosity-increasing agent," and "component (b) is added" all signal the addition of a new, distinct substance—one that is not already present in the dosage form as hardening polymer (C). Plaintiffs counter that these phrases are broad enough to encompass the addition of a greater *amount* of polymer (C), rather than the addition of a new substance. (Pls.' Opening Br. 22–23.) But the language of the specification—which discusses "adding" "further agents" and "component[s]" rather than additional amounts of substances already present—provides little support for this interpretation.

Plaintiffs also argue that because the specification notes the viscous nature of certain substances that are suitable as polymer (C), it contemplates that those substances may also serve as viscosity-increasing agent (b). The specification states: "Thermoplastic polyalkylene oxides, such as polyethylene oxides . . . are very particularly preferred [as polymer (C)]. These polymers have a viscosity at 25° C. of 4500 to 17600 cP . . . ." '060 Patent at 5:65–6:3. But the specification's passing reference to the viscosity of certain polymers does not eviscerate the importance of the numerous other statements that focus on the addition of a new substance. *See Takeda Pharm. Co. Ltd.*, 743 F.3d at 1365 (concluding that the use of the phrase "about 400 μm" three times in the specification did not defeat stronger evidence that particle size could not exceed 400 μm). For example, almost immediately after the specification describes the viscosity of thermoplastic polyalkylene oxides, it goes on to state that the dosage form may "contain further agents which complicate or prevent abuse as auxiliary substances (B)." '060 Patent at 6:33–34. Nowhere in that passage does the specification even hint that the viscous quality of thermoplastic polyalkylene oxides makes them suitable as auxiliary substances (B). Rather, the use of the phrase "contain further agents" indicates that something *besides* polymer (C) is required, regardless of that polymer's own viscosity.

Plaintiffs also point to claim 24, which provides that hardening polymer (C) may serve as a controlled release matrix material in addition to conferring the 500 Newton breaking strength required by claim 1. '060 Patent at 16:44–47, 22:65–67. According to plaintiffs, this demonstrates that the patentees intended polymer (C) to serve multiple functions, including that of viscosity-increasing agent (b). Plaintiffs undercut their own position. The fact that the patentees expressly stated that polymer (C)

could also serve as a controlled release matrix material shows that they knew exactly how to establish dual functionality when they wanted to. *See Takeda Pharm. Co. Ltd.*, 743 F.3d at 1365 (rejecting a construction that would allow deviation in particle size in part because "the inventors knew how to express ambiguity in claim language when they so desired"). Yet the patentees never stated that polymer (C) could also serve as viscosity-increasing agent (b) or any of the other auxiliary substances (B). The patentees' express disclosure of the dual functionality of polymer (C) in the context of controlled release matrix materials does not permit the Court to extend it to an entirely different situation, given the many statements in the specification that evince the patentees' intent to require the addition of a distinct substance as agent (b).

The six examples disclosed in the specification lend further support to a construction that requires the addition of a new substance. Examples 1, 2, and 3 describe the formation of a tablet consisting of an active ingredient and PEO, one of the substances the specification identifies as a suitable hardening polymer. '060 Patent at Examples 1–3, 5:54–60. These examples disclose the tablets' breaking strength, but not their viscosity. '060 Patent at Examples 1–3. Examples 4, 5, and 6, by contrast, feature tablets consisting of an active ingredient, PEO, and xanthan, which the specification lists as a viscosity-increasing agent. *Id.* at Examples 4–6, 8:63–9:15. Each of these examples discloses both the tablets' breaking strength *and* their viscosity when combined with water. *Id.* at Examples 4–6. By discussing viscosity only when an additional, non-polymer (C) component was added, the examples further demonstrate that hardening polymer (C) cannot serve as viscosity-increasing agent (b).

Plaintiffs make a futile attempt to downplay the significance of the examples, arguing that xanthan was added merely to enable the tablets in Examples 3–5 to meet the optional "visually distinguishable" test of claim 9.[5] (Pls.' Opening Br. 22–23.) They explain that Example 1's tablet contains 200 mg of PEO and no xanthan, while Example 4's tablet features an

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[5] As discussed more fully below, claim 9 features a "gelling test" that requires the formation of a gel when the viscosity-increasing agent and the "extract obtained from the dosage form" are combined with an aqueous liquid. '060 Patent at 21:41–44. It further provides that the gel "optionally remains visually distinguishable when introduced into a further quantity of an aqueous liquid." *Id.* at 21:44–46.

identical formulation aside from the replacement of 20 mg of PEO with 20 mg of xanthan. (Pls.' Opening Br. 22.) Examples 3 and 5 exhibit a similar pattern. '060 Patent at Examples 3, 5. This "substitution" of xanthan for PEO, according to plaintiffs, allowed Examples 4 and 5 to produce a gel that remained visually distinguishable when introduced into a quantity of liquid. (Pls.' Opening Br. 22–23.) Therefore, plaintiffs argue, "either an excess of polymer (C) or the addition of xanthan can be used in the invention." (*Id.* 23.) Importantly, plaintiffs do not allege that Examples 1–3, which utilized only polymer (C), produced a dosage form viscous enough to form the gel required by claim 9. Nor can this fact be inferred from the examples themselves. Consequently, because there is no evidence that the PEO in Examples 1–3 actually functioned as viscosity-increasing agent (b), plaintiffs' argument is meritless.

In sum, the specification treats polymer (C) and viscosity-increasing agent (b) as distinct components in every instance it discusses them. *See Nystrom v. TREX Co., Inc.*, 424 F.3d 1136, 1144 (Fed. Cir. 2005) (interpreting the claim term "board" to mean "wood decking material cut from a log" because the specification consistently described it that way); *AquaTex Indus., Inc. v. Techniche Solutions*, 419 F.3d 1374, 1381–82 (Fed. Cir. 2005) (concluding, in part "based upon the teachings of the specification," that the claim term "fiberfill batting material" did not include natural fibers). Accordingly, the Court construes the disputed term in claim 9 to mean: "A dosage form according to claim 1, which additionally comprises at least one of the following components a)-f): . . . (b) at least one viscosity-increasing agent different from the synthetic or natural polymer (C) of claim 1 . . . ."

2. *Viscosity-increasing agent (b) is not limited to the list of substances in the specification*

Having concluded that viscosity-increasing agent (b) cannot be the same substance as hardening polymer (C), the Court now considers Teva's argument that agent (b) is limited to a list of specific substances set out in the specification. (Defs.' Opening Br. 18–19.) That passage provides:

> If component (b) is added to the dosage form according to the invention, one or more viscosity-increasing agents are used which are selected from the group consisting of microcrystalline cellulose with 11 wt. % carboxymethylcellulose sodium (Avicel®

> RC 591), carboxymethylcellulose sodium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), locust bean flour Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-l), pectins such as citrus pectin (Cesapectin® HM Medium Rapid Set), apple pectin, pectin from lemon peel, waxy maize starch (C*Gel 04201®), sodium alginate (Frimulsion ALG (E40l)®), guar flour (Frimulsion BM®, Polygum 26/1-75®), iota carrageen (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat l50®), tara bean flour (Polygum 43/10), propylene glycol alginate (Protanal-Ester SD-LB®), sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide welan gum (K1A96), xanthan gum (Xantural 180®).

'060 Patent at 8:63–9:14. Teva argues that because the specification utilizes a so-called "Markush group" formulation—"selected from the group consisting of"—it limits viscosity-increasing agent (b) of claim 9 to a list of specified alternatives. (Defs.' Opening Br. 18; Hr'g Tr. 24–25.)

It is black letter law that courts may not import limitations from the specification into the claims unless the claim language or the specification makes clear that the invention includes the limitation. *Phillips*, 415 F.3d at 1320; *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc*, 242 F.3d 1337, 1340 (Fed. Cir. 2001). The structure and language of the '060 Patent's claims indicate that claim 9 is not so limited. Claim 9 requires only that the viscosity-increasing agent, if used, "forms a gel" under certain specified conditions. '060 Patent at 21:41–46. Claim 15, which depends from claim 9, is narrower: it requires that the viscosity-increasing agent be selected from the same list of compounds set out in the specification.[6] *Id.* at 22:15–33. If the patentees really intended claim 9 to contain the same limitations as claim 15, they would have had little reason to include claim 15 in the patent. *See Abbott Labs. v. Andrx Pharm., Inc.*, 473 F.3d 1196, 1210 (Fed. Cir. 2007) ("[T]he language of the claims and [the doctrine of] claim differentiation imply that the "pharmaceutically acceptable polymer" term

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[6] Upon close inspection, a few of the trade names of the substances in claim 15 contain slight differences from those listed in the specification. No party has addressed this issue, which appears to be simply the result of typographical errors.

in claim 1 . . . encompasses more compounds than those listed in claim 3."); *see also Acumed LLC*, 483 F.3d at 806 (stating the presumption that "independent claims are presumed to have broader scope than their dependents").

Moreover, the fact that the patentees included a Markush group in the specification, '060 Patent at 8:63–9:14, provides little support for Teva's argument that claim 9 is limited to the substances set out in that group. The Federal Circuit, in a case very similar to this one, warned that "[t]he term "Markush group" does not have any meaning within the context of a written description of a patent" and cannot be used to "limit [the court's] construction to the compounds listed in the written description." *Abbott Labs.*, 473 F.3d at 1210. Teva responds that the patentees acted as their own lexicographers by defining "viscosity-increasing agent" to mean the enumerated list of substances. (Defs.' Opening Br. 18.) The specification, however, is devoid of any language "clearly express[ing] an intent" to redefine the term "viscosity-increasing agent" to encompass only the closed list of compounds. *See Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012) (internal quotation marks and citations omitted). When the patentees defined other terms in the '060 Patent, they used express language. '060 Patent at 7:53–54 ("A dosage unit is taken to mean . . . ."), 8:28–29 ("For the purposes of the present invention visually distinguishable means . . . ."), 8:41–42 ("If the gel remains visually distinguishable, this means that . . . ."). The lack of such language with respect to the disputed claim term indicates that the patentees were not acting as their own lexicographers when they included the Markush group in the specification.

Teva has not pointed to any other evidence supporting its proposed construction that claim 9's "viscosity-increasing agent" is limited to the Markush group's list of substances, and the Court cannot find any. In fact, the specification suggests that agent (b) of claim 9 is broader than the list of specified compounds. It recites a test for "verify[ing] whether a viscosity-increasing agent is suitable as component (b)." '060 Patent at 8:55–62. If the patentees intended to limit agent (b) to the specific compounds contained in the Markush group, it is difficult to understand why they would have found it necessary to devise this test.

Accordingly, the Court concludes that viscosity-increasing agent (b), as it appears in claim 9, is not limited to the list of specific substances set out in the specification at 8:63–9:14.

B. "A necessary minimum quantity of an aqueous liquid" means "an aqueous liquid in a necessary minimum quantity"

Claim 9 provides that a gel forms when the viscosity-increasing agent is combined with the extract obtained from the dosage form and "a necessary minimum quantity of an aqueous liquid." '060 Patent at 21:41–46. The Court will refer to this requirement as the "gelling test." Teva contends that "a necessary minimum quantity of an aqueous liquid" is indefinite, an argument the Court again declines to consider before trial. (Defs.' Opening Br. 20.) Plaintiffs, on the other hand, urge the Court to construe the disputed phrase to mean "10 ml of water at a temperature of 25° C." (Pls.' Opening Br. 24.)

The language of claim 9 itself offers no guidance on the meaning of "a necessary minimum quantity of an aqueous liquid," and the specification includes no explicit definition. Plaintiffs urge, however, that the meaning of the phrase is contained within a test the patentees described in the specification for verifying the suitability of a viscosity-increasing agent for use in the dosage form. That test, which the Court will refer to as the "specification test," provides:

> [T]he active ingredient is mixed with the viscosity-increasing agent and suspended in 10 ml of water at a temperature of 25° C. If this results in the formation of a gel which fulfills the above-stated conditions, the corresponding viscosity-increasing agent is suitable for preventing or averting abuse of the dosage forms according to the invention.

'060 Patent at 8:55–62.

Although using the language of the specification test to define "a necessary minimum quantity of an aqueous liquid" carries some initial appeal, it ultimately fails because the test, upon closer examination, lacks the necessary connection to claim 9. Claim 9's gelling test applies to the dosage form *as a whole*. '060 Patent at 21:37–38, 21:41–44. It states that a gel must form from the combination of the viscosity-increasing agent, a necessary minimum quantity of an aqueous liquid, and the extract obtained from the dosage form. '060

Patent at 21:41–44. The specification test, however, is designed to assess whether a particular *viscosity-increasing agent* is suitable for use in the invention. *Id.* at 8:55–57. Moreover, that test utilizes different inputs, calling for the "active ingredient" instead of the "extract obtained from the dosage form." *Compare id.* at 8:57–59, *with id.* at 21:41–44. This difference is important: the dosage form of claim 9 consists—at a minimum—of an active ingredient, a synthetic or natural polymer (C), and a viscosity-increasing agent. *Id.* at 21:5–14, 21:37–41. The specification test, however, excludes polymer (C), a substance that may influence gel formation. *See* '060 Patent at 6:2–9 (describing the high viscosity of such polymers), 8:55–59. The fact that the two tests feature different inputs that could affect the outcome indicates that they do not describe the same subject matter. Consequently, it cannot be said that a person of ordinary skill in the art would understand "a necessary minimum quantity of an aqueous liquid" in claim 9 to refer to "10 ml of water at a temperature of 25° C."

Extrinsic evidence further confirms that plaintiffs' proposed construction is incorrect. Heinrich Kugelmann, one of the inventors of the '060 Patent, was asked at his deposition whether he knew what would constitute the minimum quantity of aqueous liquid required by claim 9. He responded:

> A: So it depends, really, on the volume of the medication formulation to be examined, meaning that a smaller volume or entity of medication would require a smaller amount of aqueous liquid as opposed to a larger medication amount that would require a larger amount of aqueous liquid.
>
> Q: Does it depend on anything else besides the volume of the medication formulation?
>
> MS. SOMMERS: Objection.
>
> A: No, I don't know. I don't know. That was just an example on which, of a factor upon which it may depend.

(Ex. A. to Decl. of Steven J. Bernstein dated Feb. 14, 2014, at 81:10–21.) The fact that an inventor of the '060 Patent did not identify 10 ml of water at a temperature of 25°C as the "necessary minimum quantity of an aqueous liquid" provides yet another element to support the Court's conclusion

that plaintiffs' proposed construction is erroneous. *See Phillips*, 415 F.3d at 1317, 1324 (authorizing courts to consider inventor testimony so long it does not contradict the intrinsic evidence).

Finally, plaintiffs attempt to buttress their proposed interpretation by contending that it is consistent with the Court's prior construction of U.S. Patent No. 7,776,314 ("'314 Patent"), which recites a gelling requirement similar to that contained in the '060 Patent's claim 9. *See* '314 Patent at 11:65–12:31; (Pls.' Opening Br. 25.) Their argument misses the mark. Unlike the '060 Patent, the '314 Patent's requirement of "10 ml of water at 25° C." appears in the very language of its *claims*. '314 Patent at 12:25–28 (stating that the dosage form must comprise "at least one viscosity-increasing agent in a quantity equal to or greater than 5 mg per dosage form and such that an aqueous extract obtained from the dosage form with 10 ml of water at 25° C. forms a gel"). Moreover, the Court never construed the phrase "a necessary minimum quantity of an aqueous liquid" because that language was not part of the '314 Patent's claims. The fact that the '314 Patent specified the amount, type, and temperature of aqueous liquid required for its gelling test does not give the Court license to import those limitations into the '060 Patent.

In short, there is simply nothing in the intrinsic or extrinsic evidence that can bridge the large gap between the claim language and plaintiffs' proposed construction, which dramatically narrows "necessary minimum" to "10 ml" and "aqueous liquid" to "water," while imposing a temperature requirement of which the claim is completely devoid of reference. The Court therefore turns to the remainder of the specification for guidance on the meaning of the disputed phrase.

Although "a necessary minimum quantity of an aqueous liquid" appears four times in the '060 Patent's specification, the relevant passages merely repeat the language of claim 9 without providing any direction on its meaning. *See* '060 Patent at 6:43–46, 8:19–24, 8:28–31, 9:23–27. The three examples that discuss gelling are similarly unhelpful. Examples 4, 5, and 6 report that a gel forms when small pieces of the dosage form "are combined with water." '060 Patent at Examples 4–6. The examples do not disclose the quantity or temperature of the water. *Id.* The only guidance the examples provide, then, is that water is one example of an aqueous liquid, which the parties obviously do not dispute.

The intrinsic and extrinsic evidence, in sum, do not disclose a meaning of "a necessary minimum quantity of an aqueous liquid" beyond the words themselves. The Court therefore construes "a necessary minimum quantity of an aqueous liquid" to mean "an aqueous liquid in a necessary minimum quantity." *Cf. Alcon Research, Ltd.*, 2011 WL 3901878, at *17 (evaluating the parties' proposed constructions of "therapeutically effective amount," but declining to provide a construction that went beyond the words of the patent prior to trial). Whether this claim language "reasonably apprise[s] those skilled in the art of the scope of the invention" is a matter to be explored at trial. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1342 (Fed. Cir. 2003) (defining indefiniteness).

C. "Forms a gel with the extract obtained from the dosage form" means "forms a gel with the extract obtained from the dosage form, which gel is difficult or impossible to pass through a needle or inject"

The Court's consideration of claim 9's gelling test is not yet complete. Teva asks the Court to construe the phrase "forms a gel with the extract obtained from the dosage form." (Defs.' Opening Br. 22); *see also* '060 Patent at 21:43–44. It argues that the phrase is indefinite because the term "gel" is "rather amorphous and undefined." (Defs.' Opening Br. 22.) Again, the Court declines to rule on the claim's indefiniteness prior to trial.

Teva is correct that the patentees did not provide an express definition of "gel." And unlike the '888 Patent, the '060 Patent does not specify a quantitative measurement of viscosity. Nonetheless, the specification does offer guidance on the characteristics of the gel that claim 9 requires. It states that the claimed gel is "virtually impossible to administer safely," '060 Patent at 8:25, and that the "increased viscosity of the extract makes it more difficult or even impossible for it to be passed through a needle or injected," *id.* at 8:39–41. Examples 4, 5, and 6 also describe the difficulty of injecting the gel. They report that when pieces of the dosage form were combined with water, a "highly viscous gel is formed" and "[o]nly with great difficulty could the gel be pressed through a 0.9 mm injection cannula." '060 Patent at Examples 4–6. The examples in the specification make clear, then, that the gel of claim 9 must be difficult or impossible to pass through a needle or inject.

Plaintiffs ask the Court to construe the disputed phrase to mean "an aqueous extract obtained from the dosage form with 10 ml of water at 25° C. forms a gel." (Pls.' Opening Br. 25–26.) The Court has already considered and rejected plaintiffs' contention that the gelling test of claim 9 requires 10 ml of water at a temperature of 25° C. In addition, plaintiffs do not explain why the Court should employ the term "aqueous extract," which appears nowhere in the patent. Both the claims and the specification refer to "the extract obtained from the dosage form," and the Court cannot ascertain any reason to detach "extract" from "dosage form" and append it to "aqueous," as plaintiffs' construction would have it.[7]

For these reasons, the Court interprets "forms a gel with the extract obtained from the dosage form" to mean "forms a gel with the extract obtained from the dosage form, which gel is difficult or impossible to pass through a needle or inject."

D. The optional "visually distinguishable" claim term requires no construction

Teva has submitted the following phrase from claim 9 for construction: "which gel optionally remains visually distinguishable when introduced into a further quantity of an aqueous liquid." (Defs.' Opening Br. 23–24); *see also* '060 Patent at 21:44–46. The parties agree that this claim term is optional. (Hr'g Tr. 15–16.) Optional terms can always be omitted and do not narrow the scope of a claim. *In re Johnston*, 435 F.3d 1381, 1384 (Fed. Cir. 2006); MPEP § 2111.04 (9th ed., Mar. 2014). Both parties agree that construction of the "visually distinguishable" phrase is not necessary, but Teva nonetheless urges the Court to adopt a construction in order to "complete the record." (Hr'g Tr. 16.) Given that construction of this term would have no impact on the litigation, the Court declines to do so in the interest of judicial restraint. *See Vivid Techs., Inc.*, 200 F.3d at 803 (noting that claim terms need only be construed "to the extent necessary to resolve the controversy").

* * *

For these reasons, the Court construes claim 9 to read as follows:

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[7] At the *Markman* hearing, Teva argued for the first time that claim 9 is invalid because the term "extract obtained from the dosage form" lacks an antecedent basis. (Hr'g Tr. 40.) The Court defers judgment on this issue until trial.

9. A dosage form according to claim 1, which additionally comprises at least one of the following components a)-f):

. . .

(b) at least one viscosity-increasing agent different from the synthetic or natural polymer (C) of claim 1, which, with the assistance of an aqueous liquid in a necessary minimum quantity, forms a gel with the extract obtained from the dosage form, which gel is difficult or impossible to pass through a needle or inject, and which optionally remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

. . .

V. Conclusion

The '888 and '060 patents will now proceed to trial. On the basis of the claim construction set forth above, the Court will determine whether defendants' ANDAs infringe plaintiffs' patents and whether these patents are valid.

Dated: New York, New York
May 27, 2014

SO ORDERED:

Sidney H. Stein, U.S.D.J.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

In re: OXYCONTIN ANTITRUST LITIGATION	04-Md-1603 (SHS)
PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., and PURDUE PHARMACEUTICALS L.P., Plaintiffs, -against- AMNEAL PHARMACEUTICALS, LLC, Defendant.	13-Cv-3372 (SHS)

FINDINGS OF FACT AND CONCLUSIONS OF LAW

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

'060 Patent	U.S. Patent No. 8,309,060
'888 Patent	U.S. Patent No. 8,337,888
'963 Patent	U.S. Patent No. 6,488,963
2014 Stip.	Stipulations or Agreed Statements of Fact or Law, Joint Pretrial Order, No. 04-Md-1603, Dkt. No. 572, filed June 23, 2014
ANDA	Abbreviated New Drug Application
API	active pharmaceutical ingredient
Bastin	International Application No. WO 95/20947
C.	Celsius
cP	centipoise
CPM	chlorpheniramine maleate
FDA	U.S. Food and Drug Administration
Hoffmeister	U.S. Patent No. 4,070,494
HPMC	hypromellose K100M
Joshi	U.S. Patent Application Publication No. US 2002/0187192
NDA	New Drug Application
OROS	osmotically controlled-release oral delivery system
PEO	polyethylene oxide
PTO	U.S. Patent and Trademark Office
Royce	U.S. Patent No. 5,273,758
Shaw	U.S. Patent No. 3,980,766
USP	United States Pharmacopeia

SIDNEY H. STEIN, U.S. District Judge.

PART 1. INTRODUCTION

This action concerns the infringement and validity of United States Patent No. 8,337,888 ("the '888 Patent"), which is associated with the opioid pain reliever OxyContin. The '888 Patent claims a controlled release oral dosage form containing oxycodone that forms a gel when dissolved in an aqueous liquid. The gelling properties of the invention enable it to resist abuse by injection, snorting, and oral ingestion.

Plaintiffs, led by OxyContin manufacturer Purdue Pharma L.P., allege that defendant Amneal, which produces generic pharmaceutical products, has infringed several claims of the patent by seeking approval from the U.S. Food and Drug Administration ("FDA") to sell a generic version of OxyContin. Amneal responds that its proposed product does not infringe plaintiffs' patent and that even if it did, the asserted claims of the patent are invalid. The parties presented factual support for their contentions during a week-long bench trial before this Court.

Applying the relevant legal standards to the evidence adduced at trial, the Court concludes that although Amneal has infringed the '888 Patent, the asserted claims are invalid as obvious and indefinite.

I. THE RECORD AND RELEVANT PROCEEDINGS

A. The '888 Patent and Asserted Claims

The '888 Patent issued on December 25, 2012. (PTX 4002 [hereinafter "'888 Patent"] at (45).) It claims priority to a provisional application, Serial No. 60/310,534, filed August 6, 2001. (Stipulations or Agreed Statements of Fact or Law, Joint Pretrial Order, No. 04-Md-1603, Dkt. No. 664, filed June 23, 2014, at ¶ 24 [hereinafter "2014 Stip."].)

Purdue[1] alleges that Amneal's proposed formulation infringes claims 5, 7, 23, and 24 of the '888 Patent. Independent claim 1, from which all asserted claims depend, claims a controlled release oral dosage form containing the active pharmaceutical ingredient ("API") oxycodone and a gelling agent comprising polyethylene oxide ("PEO"). ('888 Patent at 40:22-29.) When the dosage form is dissolved in a small amount of aqueous liquid, it attains a viscosity of at least about ten centipoise ("cP"), thereby hindering attempts at injection, snorting, or swallowing. (*Id.* at 2:64-3:30, 40:22-29.) The dosage form of claim 1 also provides a therapeutic effect for at least about twelve hours when orally administered to a human patient. (*Id.* at 40:30-32.)

The asserted dependent claims specify that the aqueous liquid is water (claim 5), that the dissolved dosage form achieves a viscosity of at least about 60 cP (claim 7), and that tampering includes crushing (claim 23) or dissolution in an aqueous liquid with heating greater than 45° Celsius ("C.") (claim 24). ('888 Patent at 40:45-46, 40:51-52, 42:10-17.)

B. The 2013 Teva Trial

In September and October of 2013, the Court held a bench trial in the consolidated actions of *Purdue Pharma L.P. et al. v. Teva Pharmaceuticals USA, Inc.*, Nos. 11-Cv-2037 and 12-Cv-5083; *Purdue Pharma L.P. et al. v. IMPAX Labs., Inc.*, No. 11-Cv-2400; and *Purdue Pharma L.P. et al. v. Sandoz Inc.*, Nos. 11-Cv-4694 and 12-Cv-5082. Because the evidence presented at the 2013 trial relates to the claims and defenses at issue here, the parties have agreed to adopt the entire record as part of the factual record in this action. (Joint Pretrial Order, No. 4-Md-1603, Dkt. No. 664, filed June 23, 2014, at 20 ¶ 14.)

C. Claim Construction

After extensive briefing and a claim construction hearing, this Court issued a Claim Construction Opinion and Order in May 2014, which construed

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[1] This Opinion refers to plaintiffs collectively as "Purdue."

the patent claims at issue to resolve the parties' disputes as to their meaning. *See In re OxyContin Antitrust Litig.*, No. 04-Md-1603, 2014 WL 2198590 (S.D.N.Y. May 27, 2014) [hereinafter "*Claim Construction*"]. All parties to this action participated in litigating the claim constructions; consequently, for purposes of this trial, that Opinion and Order "define[s] the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (quotation marks omitted).

During trial, several new issues of claim construction arose that the parties had not fully presented to the Court during its earlier claim construction hearing. The Court must resolve these claim construction disputes before analyzing the infringement and validity of the '888 Patent. *See Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1362 (Fed. Cir. 1998).

D. The 2014 Trial

The bench trial in this action began on July 14, 2014. Over the course of five days, the Court heard live testimony from nine witnesses and admitted hundreds of exhibits. Purdue's expert witnesses included Dr. Martyn Davies, an expert in drug delivery systems, including the development and testing of controlled-release formulations (Davies 2013 Tr. 683-84[2]; Davies Tr. 326), and Dr. Jerry Hausman, an expert in economics and econometrics (Hausman Tr. 272). Serving as expert witnesses for Amneal were Dr. Mohan Rao, an expert in economic analysis, including commercial success (Rao 2013 Tr. 1576; Rao Tr. 657-58); Dr. Fernando Muzzio, an expert in the design, development, and analysis of pharmaceutical products and processes, as well as rheology and the measurement of viscosity (Muzzio Tr. 489); and Dr. Michael Maurin, an expert in pharmacy practice, the syringeability of drug products, and pharmaceutical formulation and testing, specifically *in vivo* and *in vitro* testing as related to therapeutic effect (Maurin Tr. 741).

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[2] Citations to "2013 Tr." refer to the transcript of the 2013 trial, No. 04-Md-1603, Dkt. Nos. 599-621.

Another defendant, Teva Pharmaceuticals USA, Inc., also participated in the 2014 trial but has since entered into a settlement with Purdue. Purdue accused Teva of infringing both the '888 Patent and U.S. Patent No. 8,309,060 ("the '060 Patent"). The '060 Patent claims an abuse-proofed dosage form with a high breaking strength that prevents crushing; it may optionally contain additional abuse-deterring components, such as gelling agents. (PTX 4000 at 6:24-48; 21:5-14, 21:37-46.) Purdue and Teva entered into a consent judgment after the conclusion of the trial. (No. 13-Cv-4606, Dkt. No. 92.) The Court therefore does not set forth findings of fact and conclusions of law regarding Teva's alleged infringement of the '888 and '060 Patents or the validity vel non of the '060 Patent. However, the Court draws on the evidence presented at trial on those issues to the extent it relates to the validity of the '888 Patent and Amneal's alleged infringement.

E. This Opinion

On the basis of the record established by the parties and the applicable law, the Court enters these findings of fact and conclusions of law pursuant to Rule 52(a) of the Federal Rules of Civil Procedure. To the extent that any findings of fact may be deemed conclusions of law, they shall also be considered conclusions of law; to the extent that any conclusions of law may be deemed findings of fact, they shall also be considered findings of fact. *Cf. Miller v. Fenton*, 474 U.S. 104, 113-14 (1985).

II. LEGAL STANDARDS[3]

A. Procedural Context and the Hatch-Waxman Act

This litigation arises under the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C.

[3] Except where the law has evolved, the following discussion is taken largely from the Court's findings of fact and conclusions of law resulting from the 2013 trial. *See In re OxyContin Antitrust Litig.*, 994 F. Supp. 2d 367, 378-84 (S.D.N.Y. 2014).

§§ 301 *et seq.*) ("Hatch-Waxman Act"). The Hatch-Waxman Act provides a streamlined regulatory pathway for generic pharmaceutical companies to seek approval of their drugs, while giving branded pharmaceutical companies an opportunity to sue to defeat approval of the generic drugs.

Pursuant to the Hatch-Waxman Act, a pharmaceutical company can seek FDA approval for a generic drug based on an already-approved branded drug by filing an Abbreviated New Drug Application ("ANDA"). 21 U.S.C. § 355(j)(2)(A), (8)(B). As the name suggests, an ANDA does not require the detailed showings necessary for the pioneer New Drug Application ("NDA"), such as proof of safety and effectiveness. *See id.* Where a branded manufacturer's patent has not yet expired but a generic manufacturer nonetheless wants to enter the market, the generic must file a pre-expiration challenge (known colloquially as a "Paragraph IV" certification, after the relevant paragraph number in the legislation). *Id.* § 355(j)(2)(A)(vii)(IV). A generic firm's Paragraph IV certification must establish bioequivalence of the proposed generic version with the approved branded version of the drug. *See* 21 C.F.R. § 314.94(a)(9). The Paragraph IV certification must also state and explain at least one of the following claims: that the generic product would not infringe the branded firm's patent, or that the branded firm's patent is invalid. *See* 21 U.S.C. § 355(j)(2)(B)(iv)(II).

As the U.S. Court of Appeals for the Second Circuit has explained, the mere filing of "[a]n ANDA-IV certification itself constitutes an act of infringement, triggering the branded manufacturer's right to sue." *Ark. Carpenters Health & Welfare Fund v. Bayer AG*, 604 F.3d 98, 101 (2d Cir. 2010) (citing 35 U.S.C. § 271(e)(2)(A)). When a branded manufacturer files suit pursuant to that right within 45 days of receiving notice of the Paragraph IV certification, the litigation automatically stays the generic's entry to the market. 21 U.S.C. § 355(j)(5)(B)(iii). At its core, then, the Hatch-Waxman Act "redistributes the relative risks between the patent holder and the generic manufacturer, allowing generic manufacturers to challenge the validity of the patent without incurring the costs of market entry or the risks of damages from

infringement." *Ark. Carpenters Health & Welfare Fund*, 604 F.3d at 101. More significantly for purposes of this litigation, this structure allows the parties to try the dueling issues of patent infringement and patent invalidity simultaneously.

B. Claim Construction

"[T]he claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips*, 415 F.3d at 1312 (quotation marks omitted). "Generally, a claim term is given the ordinary and customary meaning as understood by a person of ordinary skill in the art at the time of invention." *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1339 (Fed. Cir. 2014).

Because ordinary and customary meaning cannot be determined "in a vacuum," the Federal Circuit has stressed "the importance of intrinsic evidence" to claim construction. *Phillips*, 415 F.3d at 1313, 1317 (quotation marks and citations omitted). The analysis "must begin and remain centered on the claim language itself." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004) (quotation marks and alterations omitted). "Claims, however, must be construed in light of the appropriate context in which the claim term is used." *Aventis Pharm. Inc. v. Amino Chems. Ltd.*, 715 F.3d 1363, 1373 (Fed. Cir. 2013). That context includes the specification, which "is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (quotation marks and citation omitted).

The prosecution history also constitutes intrinsic evidence and "has an important role in claim construction by supplying context to the claim language." *Aventis*, 715 F.3d at 1373. Because the prosecution history "represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation," it is often less helpful than the specification for purposes of claim construction. *Phillips*, 415 F.3d at 1317.

Nonetheless, the prosecution history may "provide[] evidence of how the PTO and the inventor understood the patent." *Id.*

Courts may also look to extrinsic evidence—"all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317 (quotation marks and citations omitted). Such evidence, however, may not be used "to contradict claim meaning that is unambiguous in light of the intrinsic evidence." *Id.* at 1324. "Ultimately, the construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Takeda Pharm. Co. Ltd. v. Zydus Pharm. USA, Inc.*, 743 F.3d 1359, 1363 (Fed. Cir. 2014) (quotation marks, citations, and alterations omitted).

Although claim construction is a question of law, it often presents subsidiary factual issues where, as here, the court must consult extrinsic evidence to understand the underlying science or the meaning of a term of art. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015).

C. Claims of Patent Infringement

Patent infringement "is an issue of fact, which the patentee must prove by a preponderance of the evidence." *Siemens Med. Solutions USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1279 (Fed. Cir. 2011). "In order to prove infringement, a patentee must show that every limitation of the claims asserted to be infringed is found in the accused device." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1565 (Fed. Cir. 1997).

The infringement inquiry involves two steps: (1) "the claim must be properly construed to determine its scope and meaning" and (2) "the claim as properly construed must be compared to the accused device or process." *Absolute Software, Inc. v. Stealth Signal, Inc.*, 659 F.3d 1121, 1129 (Fed. Cir. 2011) (quotation marks omitted). The Court's Claim Construction Opinion and Order of May 27, 2014, as well as the Court's resolution of other outstanding claim construction disputes *infra*, embody the first step.

"The second step in [this two-step] analysis is to apply the claims to the accused device." *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1345 (Fed. Cir. 2002). Because the allegedly infringing product in a Hatch-Waxman Act case is not yet on the commercial market, the infringement inquiry focuses on what is likely to be sold following FDA approval. *See Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). The accused device infringes a claim "when each of the claim limitations 'reads on,' or in other words is found in, the accused device." *Id.* A patentee may prove infringement by either direct or circumstantial evidence. *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1326 (Fed. Cir. 2009).

D. The Affirmative Defense of Patent Invalidity

A defendant "in any action involving . . . infringement of a patent" may plead as an affirmative defense that the asserted patent is invalid. 35 U.S.C. § 282(b)(2)-(3); *see also Microsoft Corp. v. i4i L.P.*, 131 S. Ct. 2238, 2242 (2011). Because "[a] patent shall be presumed valid," "[t]he burden of establishing invalidity . . . rest[s] on the party asserting such invalidity." 35 U.S.C. § 282(a). A defendant asserting patent invalidity must demonstrate invalidity by clear and convincing evidence. *Microsoft Corp.*, 131 S. Ct. at 2242.

1. Novelty and Anticipation

An invention must be novel in order to receive a valid patent. 35 U.S.C. § 102(a) (2006). "Invalidity based on lack of novelty (often called 'anticipation') requires that the same invention, including each element and limitation of the claims, was known or used by others before it was invented by the patentee." *Hoover Grp., Inc. v. Custom Metalcraft, Inc.*, 66 F.3d 299, 302 (Fed. Cir. 1995). A patent is therefore invalid due to anticipation when "a single prior art reference . . . expressly or inherently disclose[s] each claim limitation." *Finisar Corp. v. DirecTV Grp., Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). The doctrine's application is encapsulated in the old chestnut: "[t]hat which infringes, if later, would anticipate, if earlier." *Upsher-Smith Labs., Inc. v. Pamlab, LLC*, 412 F.3d

1319, 1322 (Fed. Cir. 2005) (quoting *Peters v. Active Mfg. Co.*, 129 U.S. 530, 537 (1889) (internal quotation marks omitted)).

The anticipating reference need not explicitly spell out each element of the anticipated patent claim, but rather can teach a claim limitation if the "teaching is inherent in the [] prior art reference." *Corning Glass Works v. Sumitomo Elec. USA, Inc.*, 868 F.2d 1251, 1262 (Fed. Cir. 1989). To show inherent anticipation, a defendant must demonstrate clearly and convincingly that a claim limitation not disclosed in the anticipating reference will always be present when the prior art is practiced as taught in that reference. *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995). "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present" in the anticipating reference. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002).

Anticipation and its subsidiary issues are questions of fact. *Amkor Tech., Inc. v. Int'l Trade Comm'n*, 692 F.3d 1250, 1254 (Fed. Cir. 2012) (anticipation); *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1328 (Fed. Cir. 2001) (inherency).

2. Obviousness and Nonobviousness

A patent for an invention may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (2006). "The ultimate judgment of obviousness is a legal determination." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). That legal determination rests on "underlying factual inquiries including: (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) objective indicia of nonobviousness." *Pregis Corp. v. Kappos*, 700 F.3d 1348, 1354 (Fed. Cir. 2012); *see also Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

For purposes of obviousness, the hypothetical person of skill in the art is presumed to know all of the teachings of the prior art in the field of the invention at the time of the patent's priority date. *See, e.g., In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Moreover, "[a] reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1379-80 (Fed. Cir. 2007) (quotation marks and citation omitted).

"Generally, a party seeking to invalidate a patent as obvious must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706 (Fed. Cir. 2012) (quotation marks omitted). The court may "look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. The overall obviousness inquiry must remain "expansive and flexible," and "a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 415, 418.

In assessing obviousness, courts must avoid the use of hindsight and ought not "simply retrace[] the path of the inventor." *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). To guard against the prejudice of hindsight bias, the court must consider objective indicia of nonobviousness. *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 711 F.3d 1348, 1368 (Fed. Cir. 2013). "Objective evidence of nonobviousness can include copying, long felt but unsolved need, failure of others, commercial

success, unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans before the invention." *Id.* In order for commercial success to provide an objective indication of nonobviousness, the patentee must demonstrate that the success of the commercial product arises from the patent claims at issue. *See, e.g., King Pharm., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1281 (Fed. Cir. 2010); *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000) ("A nexus between commercial success and the claimed features is required."). And in considering whether there was "a long-felt, unmet need" that the invention satisfied, the starting point is "the date of an articulated identified problem and evidence of efforts to solve that problem." *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332-33 (Fed. Cir. 2009).

3. Definiteness

A valid patent must "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." 35 U.S.C. § 112 (2006). The requirement of definiteness entails a "delicate balance." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2128 (2014) (quotation marks omitted). "Some modicum of uncertainty" is inevitable, and a patent is not indefinite merely because "readers could reasonably interpret the claim's scope differently." *Id.* at 2128. However, the patent "must be precise enough to afford clear notice of what is claimed." *Id.* at 2130. Therefore, "a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Id.* at 2124. This standard "mandates clarity, while recognizing that absolute precision is unattainable." *Id.* at 2129.

Indefiniteness problems may arise when "results can dramatically differ according to which of several quantitative techniques for applying a claim term is chosen, and the patent does not make clear which technique is meant." *Frans Nooren Afdichtingssystemen B.V. v. Stopaq Amcorr Inc.*, 744 F.3d 715, 724 (Fed.

Cir. 2014). In other words, if the choice of measurement technique or sample preparation method determines whether or not an accused product falls within the scope of a patent's claims, and the ordinarily skilled artisan cannot discern any guidance on which method or technique to utilize, the patent is invalid for indefiniteness. *See Takeda*, 743 F.3d at 1366, 1367 & n.4; *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1254-55 (Fed. Cir. 2008); *Howmedica Osteonics Corp. v. Tranquil Prospects, Ltd.*, 401 F.3d 1367, 1371 (Fed. Cir. 2005); *Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1339-40 (Fed. Cir. 2003); *In re OxyContin Antitrust Litig.*, 994 F. Supp. 2d 367, 433-35 (S.D.N.Y. 2014).

Although patent indefiniteness is a question of law that is intricately related to claim construction, *see Cordis Corp. v. Boston Sci. Corp.*, 561 F.3d 1319, 1331 (Fed. Cir. 2009), courts may make factual findings in support of their legal conclusions, *see HTC Corp. v. IPCom GmbH & Co., KG*, 667 F.3d 1270, 1279 (Fed. Cir. 2012) (noting that such factual findings are reviewed for clear error).

E. Attorney's Fees

In a lawsuit for patent infringement, "[t]he court in exceptional cases may award reasonable attorney fees to the prevailing party." 35 U.S.C. § 285. The U.S. Supreme Court has explained section 285's limitation to "exceptional cases" in this way:

> An "exceptional" case is simply one that stands out from others with respect to the substantive strength of a party's litigating position (considering both the governing law and the facts of the case) or the unreasonable manner in which the case was litigated. District courts may determine whether a case is "exceptional" in the case-by-case exercise of their discretion, considering the totality of the circumstances.

Octane Fitness, LLC v. ICON Health & Fitness, 134 S. Ct. 1749, 1756 (2014). In order for a court to award fees to the prevailing party, that party must demonstrate by a preponderance of the evidence that the case is exceptional. *See id.* at 1758.

PART 2. FINDINGS OF FACT AND CONCLUSIONS OF LAW

I. CLAIM CONSTRUCTION

In its Claim Construction Opinion and Order, the Court construed independent claim 1 of the '888 Patent as follows:

> 1. A controlled release oral dosage form comprising:
>
> . . .
>
> a gelling agent comprising polyethylene oxide in an effective amount to impart a viscosity of at least about 10 cP when the dosage form is subjected to tampering by dissolution in from about 0.5 to about 10 ml of an aqueous liquid; such dissolution having optionally been accompanied by tampering with the dosage form through mechanical, thermal, and/or chemical means of manipulation which changes the physical properties of the dosage form, e.g., to liberate the opioid agonist for immediate release if it is in sustained release form, or to make the opioid agonist available for inappropriate use such as administration by an alternate route, e.g. parenterally; the tampering can be, e.g., by means of crushing, shearing, grinding, chewing, dissolution in a solvent, heating (e.g., greater than about 45° C.), or any combination thereof;
>
> . . .

Claim Construction, 2014 WL 2198590, at *5-6.

During trial, two additional claim construction issues arose that the Court must resolve before addressing the infringement and validity of the '888 Patent. First, the parties disagree on the method an ordinarily skilled artisan would use to assess whether the 10 cP viscosity limitation—which the Court will refer to as the "viscosity test"—has been met. Specifically, their dispute concerns the appropriate shear rate, tampering temperature, testing temperature, and extent of dissolution. Second, the parties disagree on which substance must impart the requisite 10 cP of viscosity: Amneal contends that it

is the PEO alone, while Purdue argues that it is the "gelling agent" more broadly, which must include PEO but may also comprise other substances.

The Court must construe the '888 Patent from the perspective of a person of ordinary skill in the art. *See, e.g.*, *Teva Pharm. USA, Inc.*, 135 S. Ct. at 841. The parties agree that for purposes of this litigation, an ordinarily skilled artisan has a degree in one or more fields of medicine, chemical engineering, chemistry, pharmaceutical science, polymer chemistry, pharmaceutics, pharmaceutical technology, pharmacokinetics, and/or pharmacology, and/or a number of years of industry training or experience in one or more of those fields. (Tr. 1033-34.)

A. Method of Testing Viscosity

Independent claim 1 provides that the dosage form must attain a viscosity of at least about 10 cP when dissolved in about 0.5 to about 10 milliliters of an aqueous liquid. ('888 Patent at 40:25-29.) All of the asserted claims of the '888 Patent depend from claim 1 and therefore incorporate this viscosity test. Claim 7 specifies that a viscosity of at least about 60 cP is required. (*Id.* at 40:51-52.)

The parties agree that a person of skill in the art would conduct the viscosity test using a standard piece of laboratory equipment known as a rheometer.[4] (Davies Tr. 344; Muzzio Tr. 608.) Rheometers feature a spindle that fits inside a cup, which is filled with the liquid whose viscosity is being tested. (Davies Tr. 360; Muzzio Tr. 510.) The width of the gap between the cup and the spindle varies. (*See* Muzzio Tr. 510.) As the spindle rotates inside the cup, the rheometer measures the liquid's resistance to the movement of the spindle. (Davies Tr. 360.) The more viscous the liquid, the greater its resistance and the

[4] Although the parties and witnesses to the trial often used the terms "viscometer" and "rheometer" interchangeably (*see, e.g.*, Maurin Tr. 885), it appears that the latter is the relevant instrument for purposes of the '888 Patent and that all experts used rheometers in their tests (*id.*; Muzzio Tr. 653).

more force needed to make it flow. (*Id.*) Viscosity is expressed in a unit of measurement known as centipoise. (*Id.* 340.)

The parties disagree as to the guidance the patent provides on a number of testing parameters that may affect viscosity. The '888 Patent's claims do not expressly identify the shear rate that should be employed, the temperature at which the dissolved dosage form should be tampered or tested, or the extent to which the dosage form must be dissolved. Purdue proposes specific values for each of these variables, while Amneal contends that the patent's viscosity test embraces a much wider range of reasonable choices.

1. The viscosity test is not limited to zero shear viscosity and includes, at a minimum, shear rates ranging from .01 to 100 reciprocal seconds.

The dosage forms contemplated by the '888 Patent are pseudo-plastic, non-Newtonian solutions, which means that their viscosity depends to some degree on shear rate. (Davies Tr. 360-61; Muzzio Tr. 511, 513-14.) In mathematical terms, shear rate equals the speed of the rotating spindle divided by the distance between the spindle and the cup. (Muzzio Tr. 511; *see* PTX 4232 at PRF0029326.) Shear rate is expressed in reciprocal seconds. (*See, e.g.*, Davies Tr. 416; Muzzio Tr. 499.) As illustrated by Figure 1 below, pseudo-plastic solutions follow a viscosity curve that features three "regions" corresponding to shear rate. (Davies Tr. 972-73; PTX 4232 at PRF0029330.) At very low shear rates, viscosity is independent of shear rate, as shown by the plateau in region I; this region is also known as "zero shear viscosity." (Davies Tr. 361, 972; PTX 4232 at PRF0029329-30.) Notably, zero shear viscosity (or "zero shear") spans a range of shear rates. (Davies Tr. 928-29.) In region II, viscosity decreases dramatically as shear rate increases. (Davies Tr. 360-61, 972; PTX 4232 at PRF0029329-30.) At the very high shear rates of region III, however, viscosity levels out and again becomes independent of shear rate. (Davies Tr. 972-73; PTX 4232 at PRF0029329-30.)

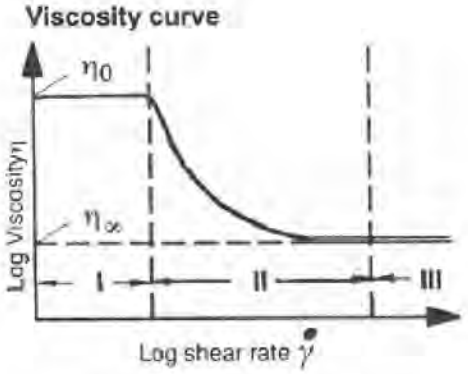

Figure 1 (PTX 4232 at PRF0029330)

Purdue argues that an ordinarily skilled artisan practicing the '888 Patent would measure viscosity at zero shear. Amneal, on the other hand, contends that the patent provides no guidance on shear rate and that persons of skill in the art could reasonably measure viscosity over a much wider range of shear rates.

The Court turns first to the claim language and the specification, which nowhere mention the term shear rate. Nor do they provide information from which shear rate can be determined, namely rheometer model, cup size, spindle size, and test speed. (Muzzio Tr. 514; *see* DTX 9173 at 0021.)

Example 3 contains the specification's only detailed description of the viscosity test, and it too is silent on shear rate. The example explains that when a placebo OxyContin tablet was mixed with citrus pectin (a gelling agent) and small amounts of water, "all the extracts were hard or difficult to pull into an insulin syringe." ('888 Patent at 32:3-6, 32:26-27.) In Purdue's view, Example 3 proves that the patent requires the use of zero shear viscosity because the solutions were in a static state at the time they were pulled into the syringe, and the viscosity of solutions at rest is comparable to their viscosity at zero shear. (Davies Tr. 929-30.) But an unspoken limitation from a single example in the specification does not serve to narrow the scope of claim 1. *See SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001). The '888 Patent contemplates abuse by injection, snorting, and oral

ingestion ('888 Patent at 2:44-47, 2:64-3:1), and the Court has heard no evidence that all three methods of abuse necessarily require solutions at rest. Even if they did, there is little reason to believe that ordinarily skilled artisan would be aware of that fact and therefore interpret claim 1 to require the use of zero shear.

Because neither the claim language nor the specification provide any guidance on shear rate, the Court must resort to extrinsic evidence to construe the claim. Purdue relies heavily on a rheology textbook by Schramm to support its zero shear construction. Schramm describes the pseudo-plastic viscosity curve and states that at very low shear rates (region I in Figure 1), liquids have a viscosity "independent of shear rate—often called the 'zero shear viscosity.'" (PTX 4232 at PRF00229329.) Schramm teaches that as a result, "most fluids" have very similar viscosities at shear rates between .001 and .01 reciprocal seconds. (*Id.*) Similarly, because viscosity is also independent of shear rate at very high shear rates (region III in Figure 1), Schramm states that "one may expect" that the viscosity at 100 reciprocal seconds "would be similar to the viscosity at a shear rate ten times higher." (*Id.*) According to Purdue, ordinarily skilled artisans would conduct the viscosity test at a range of shear rates up to 100 reciprocal seconds in order to locate zero shear, but they would consider only the viscosity values that fell within that zero shear region to be relevant for purposes of the '888 Patent.

Purdue reads the Schramm reference for far more than it is worth. Schramm never states that zero shear serves as the default when shear rate is not specified, nor does it grant zero shear preferred status among the three viscosity regions it describes. Purdue incorrectly asserts that zero shear is the only one of the three viscosity regions that Schramm identifies by a term of art, as region III is (somewhat confusingly) called the "second Newtonian range." (PTX 4232 at PRF00229329-30.) For these reasons, the Court finds that Schramm does not support the proposition that persons of skill in the art understand that the viscosity of pseudo-plastic solutions should be measured at zero shear.

In the end, the only evidence that supports Purdue's position is its own expert's testimony. At trial, Davies cited only Schramm in support of his opinion; and notably, in his deposition, Davies could not identify a single piece of scientific literature that substantiated his view. (Davies Tr. 971.) If persons of skill in the art truly regarded zero shear as the definitive shear rate for testing the viscosity of pseudo-plastic solutions, Purdue could be expected to have adduced at least some authoritative evidence to prove it.[5]

On the basis of the intrinsic and extrinsic evidence, the Court concludes that claim 1 is not confined to zero shear and that a person of ordinary skill in the art could therefore reasonably measure viscosity across a broader range of shear rates. At the barest minimum, an ordinarily skilled artisan would interpret this range as encompassing .01 to 100 reciprocal seconds—the approximate upper and lower bounds, respectively, of region I and region III of Schramm's viscosity curve. (PTX 4232 at PRF00229329-30.) Because Schramm implies that not all pseudo-plastic solutions conform to these exact contours of the viscosity curve (*id.* at PRF00229329), however, a person of skill in the art would also understand that more extreme shear rates may be relevant.[6] The evidence before the Court simply does not allow it to ascertain

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[5] In its post-trial submissions, Purdue cited an article by Bailey on the properties of PEO in aqueous solutions to support its argument that ordinarily skilled artisans measure viscosity at zero shear. (DTX 2019.) Bailey states that it determined the "[i]ntrinsic viscosities" of PEO and other polymer solutions "by extrapolation of zero shear rate reduced viscosities to infinite dilution." (*Id.* at 0001.) No expert at trial testified on the meaning of intrinsic viscosity, which appears to be a specific type or measure of viscosity. There is no other evidence in the record from which the Court can conclude that intrinsic viscosity corresponds to the '888 Patent's viscosity test. Moreover, the article did not confine its testing to zero shear but also reported viscosity "at high shear rates." (*Id.* at 0005.) Consequently, the Court finds that the Bailey reference does not lend support to Purdue's proposed claim construction.

[6] Indeed, the zero shear region for many of the tablets Davies tested fell outside .001 to .01 reciprocal seconds (Davies Tr. 369, 928-29), the range that Schramm identifies as

the precise boundaries of the acceptable range. Whether this renders the claim indefinite, as Amneal argues, is an issue the Court will confront in the invalidity portion of this Opinion, *infra*.

2. Tampering temperature is not limited to 25° C. and includes temperatures above 45° C.

The Court must next determine the temperature at which the dosage form should be tampered by dissolution, *i.e.*, dissolved. Purdue contends that because the claims do not explicitly identify a tampering temperature, persons of skill in the art would employ what Purdue asserts is the scientific convention of 25° C., or approximate room temperature. Amneal, by contrast, argues that the patent provides no guidance on tampering temperature and that a range of temperatures are therefore reasonable.

The language and structure of the '888 Patent's claims establish that tampering temperature is not limited to 25° C. Claim 24, which depends from claim 1, recites that "the dosage form is subjected to tampering by dissolution in the aqueous liquid with heating greater than 45° C." ('888 Patent at 42:16-17.) Under the doctrine of claim differentiation, dependent claims are presumed to have a more limited scope than independent claims. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012). Because claim 24 presumptively does not include subject matter that claim 1 prohibits, claim 1 necessarily encompasses tampering temperatures above 45° C. The Court can discern no evidence in the specification or prosecution history that the patentees intended to disavow this general rule.

The specification also confirms that Purdue's proposed construction is incorrect. In its Claim Construction Opinion and Order, the Court construed claim 1 as optionally including heating "greater than about 45° C." *Claim*

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the zero shear region for "most fluids" (PTX 4232 at PRF00229329). Similarly, some of the tablets had not yet reached region III at shear rates of 100 reciprocal seconds (Davies Tr. 973), the lower limit that Schramm identifies for that viscosity region (PTX 4232 at PRF00229329).

Construction, 2014 WL 2198590, at *5. The Court based this construction on the specification's definition of "tampered dosage form." ('888 Patent at 4:15-25.) In fact, in its claim construction brief, Purdue urged the Court to adopt this exact construction. (Pls.' Opening Claim Construction Br., 13-Cv-3372, Dkt. No. 15, at 11.) Its newfound conviction that claim 1 is limited to tampering at 25° C. fails in light of the patent's clear guidance on this issue.

Based on the intrinsic evidence, the Court concludes that tampering temperature for purposes of claim 1 is not limited to 25° C. and includes temperatures above 45° C. As with shear rate, however, the Court is not able to discern the exact upper and lower limits of the range of tampering temperatures that the claim allows.

3. Testing temperature is not limited to 25° C. but does not extend to temperatures at or near boiling.

The parties also dispute the temperature at which viscosity should be tested. Purdue argues that because the claims do not specify a particular testing temperature, persons of skill in the art would follow what Purdue asserts is the scientific convention of measuring viscosity at room temperature or 25° C. Amneal again contends that the patent provides no guidance on this issue and that the viscosity test permits a much wider range of testing temperatures.

The language of the claims do not provide any guidance on testing temperature. Although claim 24 requires "heating greater than 45° C." ('888 Patent at 42:15-17), it is undisputed that this 45° C. limitation refers only to tampering temperature.

The specification provides slightly more direction by suggesting that the viscosity test should not be conducted at temperatures approaching boiling. The specification explains that the invention is designed to reduce abuse by injection, inhalation, and oral ingestion. ('888 Patent at 2:18-26, 2:44-47, 2:64-3:1.) It also states that drug abusers may dissolve and heat the dosage form in order to make it more suitable for injection, inhalation, and oral consumption. ('888 Patent at 5:31-35.) An ordinarily skilled artisan would understand as a

matter of common sense, however, that abusers do not inject, snort, or swallow extremely hot liquids. While the specification provides no guidance on how hot is too hot, it is obvious that, at the very least, abusers would not administer solutions at or near boiling temperature.

Because the specification does not identify the temperature or range of temperatures that *should* be utilized, the Court must turn to extrinsic evidence. The parties disagree on the guidance provided by the United States Pharmacopeia ("USP"), a standard reference monograph for pharmaceutical scientists. (Davies Tr. 350.) In its section titled "General Notices," the USP states that "all measurements are made at 25° unless otherwise indicated." (PTX 4233 at PRF0029337.) Purdue argues that this passage proves that an ordinarily skilled artisan would conduct the '888 Patent's viscosity test at 25° C. Amneal vigorously disagrees, pointing out that another section of the USP titled "Viscosity" provides that "[t]he specifying of temperature is important because viscosity changes with temperature." (DTX 9149 at 0018.)

The Court agrees with Amneal that persons of skill in the art would not interpret the USP to prescribe a generally applicable testing temperature of 25° C. The USP states that its "General Notices" section provides "the basic guidelines for the interpretation and application of the standards, tests, assays, and other specifications of the *United States Pharmacopeia* and eliminate the need to repeat throughout the book those requirements that are pertinent in numerous instances." (*Id.* at 0005.) By its plain terms, then, the USP's default testing temperature of 25° C. only applies to the content of the USP itself;[7] the General Notices section does not purport to set forth a conventional testing temperature that readers should utilize in all contexts. In fact, the USP's explicit warning that temperature should be specified teaches away from a conclusion

[7] As Davies himself testified, the General Notices section "aids or guides the pharmaceutical scientist in undertaking the tests described in the USP." (Davies Tr. 350.)

that persons of skill in the art know that an unstated temperature equates to 25° C.

The testimony and practice of the expert witnesses also tilts against Purdue's proposed construction. Although Davies opined that pharmaceutical scientists conduct tests at 25° C. when no other temperature is specified, he cited only the USP's General Notices section in support. (Davies Tr. 350-51, 362-63.) Muzzio disagreed with Davies, stating that the choice of testing temperature depends on the particular application at issue. (Muzzio Tr. 499, 528.) And although Maurin conducted his viscosity tests at 25°, he opined that Muzzio's decision to test at temperatures between 20° and 60° was a reasonable interpretation of the '888 Patent. (Maurin Tr. 883-84.) Because the opinions of Maurin and Muzzio are more consistent with the '888 Patent's specification and the USP, the Court assigns them greater weight than Davies's testimony.

Finally, Purdue and Amneal present two additional types of extrinsic evidence that the Court declines to consider for purposes of claim construction. First, the parties attempt to support their proposed constructions with evidence on the specific temperature of solutions that addicts typically inject. But the '888 Patent contains no information on this issue, and there is no evidence to suggest that persons of skill in the art possess any independent understanding of the customary practices of drug abusers.[8] Evidence of real-world abuse conditions, at least with respect to testing temperature, therefore

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[8] Although Muzzio and Davies based their opinions of testing temperature partly on their beliefs regarding the temperature of liquids that addicts inject, they appear to have derived that knowledge from reports and testimony by drug abuse experts who served as witnesses during the 2013 trial. (Muzzio Tr. 527; Davies Tr. 988.) There is no reason to believe that persons of ordinary skill in the art, most of whom presumably have not participated in litigation involving drug abuse, would possess similar knowledge. And unlike the common sense conclusion that abusers do not administer boiling solutions, the specific temperature they *do* utilize is not a matter of common knowledge.

cannot inform the Court's conclusion on how persons of skill in the art would interpret the '888 Patent.

Second, Amneal supports its proposed construction with certain laboratory tests of Reformulated OxyContin in which Purdue measured viscosity at room temperature, 37° C., 95° C., and boiling temperature. (DTX 9169 at 0070-71; PTX 4221 at PRF1191128; Weingarten Tr. 190.) Because there is no evidence that Purdue conducted these tests in accordance with the '888 Patent as opposed to some other protocol designed to serve some other goal, the Court assigns them no weight for purposes of claim construction. (*See* Davies Tr. 468.) Even if these tests bore some relationship to the '888 Patent, the Court would disregard Purdue's use of 95° C. and boiling temperature because the intrinsic evidence forbids such testing temperatures. *See Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1382 (Fed. Cir. 2008) ("A court may look to extrinsic evidence so long as the extrinsic evidence does not contradict the meaning otherwise apparent from the intrinsic record.").

Ultimately, as with shear rate, the only real evidence that Purdue has amassed in support of its proposed claim construction consists of Davies's largely unsupported opinion that ordinarily skilled artisans simply know to test viscosity at 25° C. Because the weight of the relevant extrinsic evidence demonstrates that persons of skill in the art would not interpret the '888 Patent's silence to require a testing temperature of 25° C., the Court concludes that the viscosity test is not limited to that temperature. Although the '888 Patent clearly permits a range of testing temperatures (excluding those at or near boiling), the Court is again unable to ascertain the precise boundaries of that range.

4. The viscosity test is conducted after a visual inspection confirms that the soluble components of the dosage form have dissolved, although insoluble particles may remain.

Finally, the Court must determine the extent of dissolution that the viscosity test requires. Purdue argues that the soluble components of the

dosage form must be completely dissolved before viscosity may be tested. Amneal counters that the patent provides no guidance on the necessary extent of dissolution.

The specification's only discussion of this issue occurs in Example 3. It explains that when a placebo OxyContin tablet and citrus pectin are dissolved in water, "[t]he tablet's coating is suspended in the mixture resembling a paste. All the samples have a creamy texture and milk like color. Additionally, the filtration with cotton cannot remove the suspended material." ('888 Patent at 32:30-34.) According to the specification, the tablet's coating may include a water-insoluble material such as a wax, shellac, or zein. (*Id.* at 20:1-4.) The specification therefore instructs that the dissolved dosage form may be tested for viscosity even when insoluble components, such as the tablet's coating, remain suspended in the solution.

The testimony and practice of the expert witnesses shed additional light on this claim construction issue. Maurin, Muzzio, and Davies all conducted the viscosity test after visually inspecting the samples to determine that the soluble components had dissolved. (Muzzio Tr. 603-04; Maurin Tr. 797-98; Davies Tr. 352-53.) In light of their consistent approach, the Court credits Davies's opinion that this procedure represents standard practice. (Davies Tr. 353, 927.)

Based on the intrinsic and extrinsic evidence, the Court concludes that the viscosity test requires ordinarily skilled artisans to visually inspect samples to confirm that the soluble components of the dosage form have dissolved. Insoluble particles, however, may remain.

B. The Gelling Agent as a Whole May Confer the Requisite Viscosity.

Having clarified the method by which persons of skill in the art would conduct the '888 Patent's viscosity test, the Court must now address which substance—the "gelling agent" or PEO more specifically—must impart the requisite 10 cP of viscosity.

The Court begins with the language of the claim, which it finds to be ambiguous. It is not immediately clear whether "in an effective amount to impart a viscosity of at least about 10cP" ('888 Patent at 40:25-26) refers to PEO or the gelling agent more broadly. Although Amneal urges that its construction represents the plain and ordinary meaning of the claim, Purdue's interpretation is equally reasonable, especially in light of the fact that Amneal's construction renders the term "gelling agent" unnecessary. See *Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1257 (Fed. Cir. 2010) ("Claims must be interpreted with an eye toward giving effect to all terms in the claim.") (quotation marks and citation omitted); *In re Gabapentin Patent Litig.*, 503 F.3d 1254, 1263 (Fed. Cir. 2007).

The specification lends support to Purdue's construction by repeatedly teaching that the dosage form as whole, rather than one specific component, should be tested for the requisite viscosity. For example, the specification states that "the dosage form forms a viscous gel after the dosage form is tampered with, dissolved in an aqueous liquid . . . , causing the *resulting mixture* to have a viscosity of at least about 10 cP." ('888 Patent at 7:21-25 (emphasis added)). Similarly, the specification teaches that in some embodiments of the invention, "the dosage form forms a viscous gel after the dosage form is tampered with, dissolved in an aqueous liquid . . . and then heated (e.g., greater than about 45° C.), causing the resulting mixture to have a viscosity of at least about 10 cP." (*Id.* at 7:28-33.) These passages indicate that PEO alone need not produce the required viscosity because (1) the dissolved dosage form must achieve a viscosity of 10 cP and (2) the dosage form may include both PEO and other gelling agents.

Example 3 further suggests that the patent requires the dosage form as a whole, rather than PEO in isolation, to be tested for the necessary viscosity. In Example 3, the inventors reported the viscosity that resulted from adding citrus pectin to a placebo OxyContin tablet and small amounts of water. ('888 Patent at 32:3-25.) Importantly, the inventors tested the viscosity of a dosage form and a gelling agent (pectin) together, rather than measuring the viscosity

of pectin mixed solely with water. (*See id.* at 32:10-12.) Amneal's proposed construction would run contrary to the testing method the inventors used in Example 3 by requiring the viscosity of PEO to be measured separately from the other components of the dosage form.

The prosecution history corroborates the teachings of the specification. The '888 Patent issued from an application filed on January 12, 2012, Serial No. 13/349,449 ("the '449 Application"). (2014 Stip. ¶ 39.) Independent claim 1 of the '449 Application claimed a dosage form "further including a gelling agent in an effective amount to impart a viscosity unsuitable for administration . . . when the dosage form is crushed and mixed with from about 0.5 to about 10 ml of an aqueous liquid." (*See* DTX 9001 at 0488.) Following an interview with the Examiner, the applicants amended claim 1 in the following manner:

> ~~said dosage form further including~~ a gelling agent comprising polyethylene oxide in an effective amount to impart a viscosity of at least about 10 cP . . . when the dosage form is subjected to tampering by dissolution in ~~crushed and mixed with~~ from about 0.5 to about 10 ml of an aqueous liquid"

(*Id.*) As this amendment demonstrates, the applicants overcame the Examiner's objections to the '449 Application by clarifying that the gelling agent must "compris[e] polyethylene oxide" and by specifying a quantitative viscosity requirement of at least about 10 cP. (*See id.* at 0498; 2014 Stip. ¶ 51.)

It is clear that neither the patent applicants nor the Examiner believed that the amendment required PEO alone to impart 10 cP of viscosity. In their statement of the substance of the interview, the applicants explained that the "Examiner agreed with Applicants' position that the Kao reference (i) does not teach or suggest a gelling agent comprising polyethylene oxide, . . . and (iii) is silent as to the *dosage forms* described therein achieving a viscosity of at least 10 cP when tampered in accordance with the present invention." (DTX 9001 at 0493 (emphasis added).) This account confirms that the applicants understood that the dosage form as a whole, rather than PEO exclusively, must achieve a viscosity of at least 10 cP. Similarly, in her reasons for allowance, the Examiner

stated that "[t]he prior art does not teach or suggest the claimed invention as a controlled release dosage form comprising a drug susceptible for abuse . . . that also comprises a gelling agent to impart the viscosity unsuitable for injections or nasal administrations." (*Id.* at 0522.) Even after the applicants added the PEO limitation, then, Examiner interpreted the amended claim to mean that the gelling agent more broadly—and not PEO by itself—could produce the necessary viscosity.

Finally, expert testimony confirms that Purdue's construction is correct. Davies explained that it would be very difficult to measure the viscosity imparted by PEO alone when a tablet includes both PEO and another gelling agent (Davies Tr. 920, 1019), which the patent expressly allows ('888 Patent at 5:18-21, 40:25). Amneal agrees, admitting that "[t]here is no direct means of determining the viscosity imparted by the PEO in Amneal's products," which utilize both PEO and the gelling agent hypromellose K100M ("HPMC"). (Defs.' Responsive Post Trial Br. at 12; *see also* Muzzio Tr. 548, 553-55; 2014 Stip. ¶ 75.) The Court finds that under Amneal's proffered construction, a person of ordinary skill in the art could not determine whether a dosage form featuring both PEO and another gelling agent satisfied claim 1 because they could not isolate the amount of viscosity produced by PEO alone. It is unlikely that an ordinarily skilled artisan would interpret the claim to require something that is beyond the level of skill in the art.

In sum, the specification, prosecution history, and expert testimony confirm that the viscosity of the dissolved dosage form—which may include both PEO and other gelling agents—is what matters for purposes of claim 1. The Court therefore construes claim 1 of the '888 Patent to read:

> 1. A controlled release oral dosage form comprising:
>
> . . .
>
> a gelling agent comprising polyethylene oxide, said gelling agent in an effective amount to impart a viscosity of at least about 10 cP when

> the dosage form is subjected to tampering by dissolution in from about 0.5 to about 10 ml of an aqueous liquid. . . .

II. FACTUAL BACKGROUND: ABUSE OF OXYCONTIN AND PURDUE'S RESPONSE[9]

Now that the Court has construed the '888 Patent's claims, it must determine whether Amneal has infringed the patent and whether the patent is valid. The following factual background, which the Court bases on evidence presented at both the 2013 and 2014 trials, provides useful context for the infringement and validity analyses that follow.

Abuse of opioids is a stubborn problem that dates back centuries. (Sellers 2013 Tr. 78-80.) In the past two decades, the United States has seen a sharp rise in the abuse of prescription opioids, to such an extent that the FDA considers opioid abuse and misuse "a public health epidemic." (PTX 2157 at 4; *see generally* PTX 2189.) In 2010, prescription opioid overdoses accounted for 16,651 deaths, greater than three-quarters of all prescription drug overdose deaths in the United States. (PTX 2157 at 4.)

Among the prescription opioids at the center of that epidemic has been OxyContin, viewed by abusers as "a suitable substitute for heroin." (PTX 2147 at 1.) Approved in 1995, what OxyContin added in pharmaceutical value was its aggregate strength and extended release profile, providing sustained pain relief over an extended period of time. (Oshlack Tr. 62; Sellers 2013 Tr. 81-82.) It combined several doses worth of oxycodone—a powerful opioid—into a single tablet that released the oxycodone over time. (Sellers 2013 Tr. 81-82.) Thus, a twelve-hour extended-release OxyContin tablet holds twice as much oxycodone as a six-hour oxycodone tablet does, and it releases the API over twice as long a time period. (*See id.*)

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[9] Significant portions of this discussion are drawn from the Court's findings of fact and conclusions of law resulting from the 2013 trial. *See In re OxyContin Antitrust Litig.*, 994 F. Supp. 2d at 413-16.

The original formulation of OxyContin (which Purdue stopped selling in 2010) was susceptible to tampering, since abusers could crush the tablets easily into powder, thereby destroying the time-release aspect of the formulation and causing immediate release of the opioid. (Oshlack Tr. 46; Sellers 2013 Tr. 70-71, 74, 81-82.) If the abuser snorted the powder, or dissolved the powder into a liquid and injected the solution intravenously, then the abuser would experience an opioid "high." (PTX 2189 at 224.) The first wide-scale public acknowledgements of the trend of OxyContin abuse came in January 2001, from the Department of Justice. (*See* Sellers 2013 Tr. 82-83, 99; PTX 2147.) In July 2001, Purdue and the FDA changed the label of OxyContin to warn doctors about the potential for abusers' tampering with the dosage form. (Sellers 2013 Tr. 100-01; PTX 2148.) By 2003, the College of Problems on Drug Dependence referred to the "substantial amount of public attention" paid to OxyContin abuse, and it noted a significant increase in abuse, especially in 2001 (the most recent year for which it had complete data). (PTX 2189 at 222.)

Purdue began investigating ways to reformulate OxyContin to deter abuse. It had begun to develop abuse-deterrent technologies in 1997. (Kaiko 2013 Tr. 134.) Those initial efforts focused on other frequently abused drugs besides OxyContin and on addressing other methods of abuse besides snorting and injecting. (*Id.* at 135-36.) When the abuse of Original OxyContin drew Purdue's attention in 2001, its research and development team considered, among other ideas, creating a tablet that featured physical obstacles to tampering and abuse. (*Id.* at 154-56; *see* Oshlack Tr. 47.) One idea it had early on was to include a gelling agent in the tablet that, when the tablet was mixed with a small amount of liquid, caused the solution to form a gel too viscous to pull into a syringe. (Oshlack Tr. 49-50.)

Purdue submitted a New Drug Application ("NDA") to the FDA in November 2007, proposing a Reformulated OxyContin. (PTX 2424 at PRF2397743.) The FDA initially rejected the NDA. (*Id.*) The rejection letter suggested further studies that might overcome the deficiencies in the NDA. (*Id.* at PRF2397743-45.) Purdue obliged, conducting seven further *in vitro*

studies and producing thousands of pages of results. (Weingarten 2013 Tr. 236-38.) Those studies went into an "NDA re-submission package" in March 2009. (*Id.*; *see also* PTX 2137.) At a September 2009 briefing to the FDA Advisory Committee, Purdue explained the results, calling Reformulated OxyContin an "incremental improvement" but conceding that the impact of the abuse-proof formulation would remain unknown until it hit the market. (Weingarten 2013 Tr. 246; *see generally* PTX 1941.)

In April 2010, the FDA approved Reformulated OxyContin. (Weingarten 2013 Tr. 246; PTX 2132.) Purdue launched the new product and simultaneously discontinued sales of Original OxyContin in the United States. (Gasdia 2013 Tr. 483-84; Weingarten 2013 Tr. 247.) Reformulated OxyContin featured dual abuse deterrence mechanisms: high breaking strength (to resist crushing) and the ability to gel when mixed with water (to hinder injection and inhalation). (Weingarten Tr. 162; PTX2137A at 2-4; PTX2431 at 1156027.) Purdue believed that even if an abuser managed to crush an OxyContin tablet, the tablet's ability to gel upon contact with liquid would frustrate the abuser's attempt to achieve a high through snorting or injection. (*See* PTX2137A at 2-4.)

The 2010 market debut of Reformulated OxyContin was not marked by fanfare, because the FDA would not approve any changes to the drug's label until it saw the real-world effects of the new formulation. (Sellers 2013 Tr. 95; Weingarten 2013 Tr. 248-51.) Russell Gasdia, Purdue's Vice President for Sales and Marketing, explained during the 2013 trial that when Purdue first introduced Reformulated OxyContin on the market, "if a health care professional asked what was different between the reformulation [and] the original, the most the [sales] rep could say is the intent of the reformulation was to minimize abuse through manipulation, but that until the package insert reflected any specific information, there was nothing else they could share." (Gasdia 2013 Tr. 485; *see also* Gasdia Tr. 205.) This official silence on abuse deterrence did not mean that the market was completely ignorant: third-party analysts, trade journals, and a press release described the changes to the formulation. (Gasdia 2013 Tr. 485.)

Almost immediately upon Reformulated OxyContin's entrance in the market, Purdue and the FDA began the task of designing a post-marketing epidemiological study to understand the new product's real-world effectiveness at deterring abuse. (Weingarten 2013 Tr. 247-50; Weingarten Tr. 170-71.) Purdue undertook several long-term studies and began sending regular updates to the FDA. (Weingarten 2013 Tr. 250.) By July 2012, those updates noted reductions in OxyContin's diversion, abuse, and street price. (*Id.*; *see generally* PTX 2134.) Although abusers tried to evade the abuse-deterrent properties of the drug (Rao 2013 Tr. 1615-16), the more significant trend was abusers' substituting other opiates in the place of OxyContin (*id.* at 1614; PTX 2732). Purdue's studies also showed a significant reduction in OxyContin prescriptions written by "problematic" physicians linked to the OxyContin abuse epidemic. (Weingarten Tr. 173-74; PTX 4225 at PRF0029051-52.)

At Purdue's request, on April 16, 2013, the FDA announced that it would withdraw approval of Original OxyContin and stop accepting ANDAs that proposed generic versions of the drug. (PTX 2157 at 7; Hausman Tr. 293-94.) The FDA reasoned that, with Reformulated OxyContin available to provide the same benefits with lower risks of abuse and misuse, "the benefits of original OxyContin no longer outweigh its risks." (PTX 2157 at 7.) On the same day, the FDA approved a new label that finally allowed Purdue to market Reformulated OxyContin on the basis of its abuse-deterrent properties. (*See* PTX 2133.) The FDA's "Orange Book" lists the '888 Patent as covering Reformulated OxyContin. (2014 Stip. ¶ 59.)

III. INFRINGEMENT

For the reasons that follow, the Court concludes that Amneal infringes all asserted claims of the '888 Patent.

A. Findings of Fact

In July 2011, Amneal filed an ANDA seeking approval to market various dosage strengths of generic Reformulated OxyContin. (*See* 2014 Stip. ¶ 61.) The

Court finds that Purdue has shown by a preponderance of the evidence that Amneal's proposed tablets meet all the limitations of the asserted claims of the '888 Patent.

1. Amneal's tablets meet the limitations of claim 1 because their gelling agents impart a viscosity of at least 10 cP.

With respect to claim 1—the independent claim from which all the asserted claims depend—Amneal stipulates that its proposed tablets are controlled release oral dosage forms that contain from about 2.5 milligrams to about 320 milligrams oxycodone or a pharmaceutically acceptable salt thereof. (2014 Stip. ¶¶ 64-66, 72-73; *see* '888 Patent at 40:21-24.) Amneal further stipulates that its tablets provide a therapeutic effect for at least about 12 hours when orally administered to a human patient. (2014 Stip. ¶ 79; *see* '888 Patent at 40:30-32.)

Amneal's tablets also meet the 10 cP viscosity requirement of claim 1 as the Court has construed that claim. Amneal utilizes two different gelling agents: PEO and HPMC. (Muzzio Tr. 548; PTX 4010 at AMLOXY00408; *see* 2014 Stip. ¶ 75.) Amneal stipulates that when its tablets are subjected to tampering by dissolution in from about .5 to about 10 milliliters of an aqueous liquid, a viscosity of at least about 10 cP results. (2014 Stip. ¶ 77.) Muzzio attributed this viscosity to the gelling agents HPMC and PEO. (Muzzio Tr. 548.)

Viscosity testing by Davies confirms that Amneal's proposed tablets are significantly more viscous than 10 cP when tampered according to claim 1. (Davies Tr. 370; PTX 4198.) Davies crushed three tablets of each dosage strength and dissolved them in 30 milliliters of water at 25° C., which equates to one tablet per 10 milliliters. (Davies Tr. 348-51.) He mixed the solutions with a standard mechanical stirrer and visually inspected them to ensure that the soluble components of the dosage form had dissolved. (*Id.* at 352-53.) Davies then quantitatively measured the viscosity of each sample at 25° C. using a commercially available rheometer, whose accuracy he had verified by testing a fluid of known viscosity called a "viscosity standard." (*Id.* at 351, 359; *see also*

Muzzio Tr. 492.) All samples exceeded 10 cP at .01 to 100 reciprocal seconds, the range of shear rates that Davies utilized. (PTX 4198.)

The Court credits Davies's testing protocol as reliable, unbiased, and consistent with the teachings of the '888 Patent. In accordance with the specification's guidance on tampering, Davies crushed the tablets prior to dissolving them. (*See* '888 Patent at 4:22-25; Davies Tr. 349.) Although Davies dissolved three tablets in 30 milliliters instead of one tablet in ten milliliters, as claim 1 directs, he made that choice because the rheometer he used requires a minimum volume of 22 milliliters. (Davies Tr. 351.) The Court finds that Davies's method is equivalent to that prescribed by the '888 Patent.

To the extent the '888 Patent does not specify the exact shear rate, testing temperature, and tampering temperature that should be utilized—as discussed in the Court's claim construction, *supra*—the Court concludes that Davies's choices fall within the permissible range. There is no dispute that the patent allows tampering and testing temperatures of 25° C., and the range of shear rates that Davies utilized is consistent with the Schramm reference. (*See* PTX 4232 at PRF00229329.) Tellingly, Amneal does not take issue with Davies's methodology with respect to claim 1; its sole non-infringement argument turns on the claim construction issue regarding the "gelling agent" that the Court has already resolved.

In light of Amneal's stipulations and Davies's testing results, the Court concludes by a preponderance of the evidence that Amneal's tablets satisfy the limitations of independent claim 1.

2. Amneal's tablets meet the limitations of claim 5 because they attain a viscosity of at least about 10 cP when dissolved in water.

Dependent claim 5 claims "[t]he controlled release oral dosage form of claim 1, wherein the aqueous liquid is water." ('888 Patent at 40:45-46.) Because Davies's viscosity testing demonstrates that Amneal's tablets achieve a viscosity of at least about 10 cP when dissolved in water (Davies Tr. 349, 370;

PTX 4198), the Court concludes by a preponderance of the evidence that Amneal's tablets meet the limitations of this claim.

3. Amneal's tablets meet the limitations of claim 7 because they obtain a viscosity of at least about 60 cP.

Dependent claim 7 recites "[t]he controlled release oral dosage form of claim 1, wherein a viscosity of at least about 60 cP is imparted." ('888 Patent at 40:51-52.) Davies's tests show that all dosage strengths of Amneal's tablets achieved viscosities well above 60 cP. (Davies Tr. 370; PTX 4198.) Consequently, the Court finds by a preponderance of the evidence that Amneal's tablets meet the limitations of claim 7.

4. Amneal's tablets meet the limitations of claim 23 because they achieve the requisite viscosity when crushed and dissolved in water.

Dependent claim 23, as previously construed by the Court, claims "[t]he controlled release oral dosage form of any of claims 2, 4, 5, 6 and 7, wherein the requisite viscosity is obtained when the dosage form is subjected to tampering that includes crushing and dissolution in the specified volume of aqueous liquid." *Claim Construction*, 2014 WL 2198590, at *7. Claim 23 exhibits a "multiple dependent claim" structure because it "refers back in the alternative to more than one preceding independent or dependent claim." MPEP § 608.01(n) (9th ed., Mar. 2014). Therefore, claim 23 contains all the limitations imposed by whichever of claims 2, 4, 5, 6, or 7 is being considered. *See* 35 U.S.C. § 112(e) ("A multiple dependent claim shall be construed to incorporate by reference all the limitations of the particular claim in relation to which it is being considered."). Because Purdue does not assert claims 2, 4, and 6 against Amneal, only claims 5 and 7 are relevant to the infringement inquiry.

Davies's viscosity testing proves that Amneal's tablets satisfy all the limitations of claim 23. Davies tampered the tablets by crushing them, as claim 23 requires. (Davies Tr. 349; '888 Patent at 42:10-13.) After Davies dissolved the tablets in the required amount of water (claim 5), all dosage strengths exhibited

viscosities greater than 10 cP (claim 5) and greater than 60 cP (claim 7). (Davies Tr. 370; PTX 4198.) The Court therefore finds by a preponderance of the evidence that all the limitations of claim 23 are found in Amneal's tablets.

5. Amneal's tablets meet the limitations of claim 24 because they obtain the requisite viscosity when dissolved in water heated above 45° C.

Dependent claim 24 also features a multiple dependent structure. As construed by the Court, that claim refers to "[t]he controlled release oral dosage form of any of claims 2, 4, 5, 6 and 7, wherein the requisite viscosity is obtained when the dosage form is subjected to tampering that includes dissolution in the specified volume of aqueous liquid with heating greater than 45° C." *Claim Construction*, 2014 WL 2198590, at *7. Again, only claims 5 and 7 are relevant to the infringement inquiry here.

Purdue has met its burden of proof with respect to claim 24. First, the Court credits Davies's opinion that because all of Amneal's tablets have viscosities greater than 10 cP (claim 5) and 60 cP (claim 7) when dissolved in water at a temperature of 25° C., they would have an even higher viscosity when dissolved in water heated above 45° C., cooled to 25° C., and then tested. (Davies Tr. 923.) This is because heating the dissolved dosage forms above 45° C. would cause some of the water to evaporate and thereby increase the viscosity of the solutions. (*Id.*) Although the '888 Patent does not prescribe a specific range of testing temperatures for claim 24, there is no dispute that a testing temperature of 25° C. falls within the acceptable range.

A set of viscosity tests that Davies conducted on Amneal's 40 milligram and 60 milligram tablets also contributes to the Court's finding of infringement. Davies followed essentially the same protocol he used to test infringement of claims 1, 5, 7, and 23, except that he dissolved Amneal's tablets in water heated to 50° C. (Davies Tr. 374.) He then allowed the solutions to cool to 25° C. and measured their viscosities, which registered well above 60 cP. (*Id.* at 374-75; PTX 4199.)

Amneal contends that Purdue has not met its burden of proof because Davies did not test the remainder of Amneal's dosage strengths at tampering temperatures above 50° C. The Court disagrees. Amneal's 40 milligram and 60 milligram tablets contain the lowest and highest amounts of gelling agent (combined PEO and HPMC), respectively. (PTX 4010 at AMLOXY00408; Davies Tr. 374-75.) Since both those tablets achieved viscosities above 60 cP, the Court credits Davies's opinion that Amneal's other tablets would, too. (*Id.* 375.)

For these reasons, the Court finds by a preponderance of the evidence that all dosage strengths of Amneal's tablets meet the limitations of claim 24.

B. Conclusions of Law

Because all limitations of the asserted claims 5, 7, 23, and 24 of the '888 Patent read on Amneal's tablets, the Court concludes that Amneal infringes those claims.

IV. INVALIDITY

A. Novelty Pursuant to 35 U.S.C. § 102

Amneal has attempted to show that the '888 Patent fails to satisfy the novelty requirement of 35 U.S.C. § 102 because it is anticipated by two separate prior art references. The Court finds that Amneal has not met its burden of proof with respect to either reference.

1. Findings of Fact

a) The '963 Patent does not disclose all the limitations of the '888 Patent.

Amneal contends that the '888 Patent is invalid as anticipated by a prior art reference by Dr. James McGinity and Dr. Feng Zhang. In 1995, Dr. McGinity and Dr. Zhang developed a process for the manufacture of sustained-release tablets comprising PEO. (*See generally* Zhang 2013 Tr. 319-47.) They memorialized their work in an application to the World Intellectual Property

Organization ("the Application"), published on December 31, 1997. (DTX 2562 at (43).) McGinity and Zhang later received U.S. Patent No. 6,488,963 ("the '963 Patent") for their invention. (*See* PTX 1600.) The '963 Patent claims priority from the Application (*compare id.* at (60), *with* DTX 2562 at (30), (60)), and the parties agree that the Application is prior art to the '888 Patent (2014 Stip. ¶ 134). For purposes of this litigation, the '963 Patent is essentially equivalent to the Application, and the Court will refer to them interchangeably. (Muzzio Tr. 493; Maurin Tr. 744.) The Court made extensive factual findings on the disclosures of the '963 Patent and the Application following the 2013 trial, which it relies on here. *See In re OxyContin Antitrust Litig.*, 994 F. Supp. 2d at 421-27.

The Court previously found that the Application discloses controlled-release dosage forms containing oxycodone. *Id.* at 421, 423. The parties disagree whether it also discloses oxycodone in an amount "from about 2.5 mg to about 320 mg," which claim 1 of the '888 Patent requires. ('888 Patent at 40:23-24.) The Court credits Maurin's testimony that (1) the dosage strengths of Original OxyContin available in 2001 had between 10 and 160 milligrams of oxycodone and (2) there were no "controlled-release oxycodone products that were commercially-available before 2001" that contained less than 2.5 or more than 320 milligrams of oxycodone. (Maurin Tr. 764-65). But the fact that the pharmaceutical products on the market all contained oxycodone in amounts between 2.5 and 320 milligrams does not prove that ordinarily skilled artisans would interpret the Application to *preclude* dosage forms that fall outside that range. In other words, nothing in the Application limits this aspect of the invention to what was already extant in the art.

Amneal also relies on Example 4 of the Application, which describes tablets containing the antihistamine chlorpheniramine maleate ("CPM") and varying amounts of PEO and polyethylene glycol. (DTX 2562 at 19:5-8.) The amount of CPM was held constant at 6 weight percent, which Amneal contends falls into the '888 Patent's claimed range of about 2.5 to about 320 milligrams. (*Id.* at 19:7-8.) But Example 4 does not disclose the total weight of

the tablets; therefore, it is not possible to determine whether substituting oxycodone for CPM would result in tablets containing the necessary amount of oxycodone. If Example 4's tablets had a total weight of only 30 milligrams, for example, a 6 weight percent formulation would yield only 1.8 milligrams of oxycodone, less than the '888 Patent requires.

In sum, the Court finds that Amneal has not shown by clear and convincing evidence that the Application necessarily discloses about 2.5 to about 320 milligrams of oxycodone, as claim 1 of the '888 Patent requires. That determination ends the inquiry into whether the Application and the '963 Patent anticipate the '888 Patent. *See Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (quotation marks and citation omitted) (noting that the prior art reference must "disclose[], either expressly or inherently, all of the limitations of the claim").

b) The '591 Application does not disclose all limitations of the asserted claims of the '888 Patent.

Amneal also contends that the '888 Patent is anticipated by an application to the World Intellectual Property Organization, WO 99/44591 ("the '591 Application"), which was published in September 1999. (DTX 9003 at (43).) The '591 Application is prior art to the '888 Patent. (2014 Stip. ¶ 140.) It discloses extended release dosage forms that deliver an API at a linear rate of release. (*Id.* at 3:23-25.)

Amneal did not argue at trial that the '591 Application anticipates the '888 Patent, and the Court is reluctant to make a finding of invalidity based on testimony that was not subject to cross-examination specifically tailored to the subject of novelty. Even so, the trial evidence, which Amneal marshalled in support of an anticipation argument in its post-trial submissions, fails to meet the clear and convincing standard.

First, although Example 11 of the '591 Application expressly discloses a tablet containing PEO and 100 milligrams of oxycodone (DTX 9003 at 34:23-29, 37:1-6), it does not disclose a 12-hour therapeutic effect. It is true that the '591

Application is directed at controlled-release dosage forms and that Example 8—which sets out the composition and manufacturing process used in Example 11—states that its morphine-based tablet exhibits "a linear profile over 12 h[ou]rs at a constant rate of release." (*Id.* at 34:21-22.) But Example 11, which covers a wide range of different APIs, does not disclose any release profile and contains no *in vitro* or *in vivo* dissolution data. (*See* Maurin Tr. 898.) Even if Example 11 incorporates by reference the same 12-hour release rate of Example 8, the Court hesitates to infer that that release profile would provide the necessary therapeutic effect. (*See id.* at 896-97.) In the absence of these disclosures, the Court is unable to find by clear and convincing evidence that the dosage form of Example 11 would necessarily satisfy the therapeutic effect limitation of claim 1 of the '888 Patent. (*See* '888 Patent at 40:30-32.)

Second, even if the '591 Application disclosed the necessary therapeutic effect, Amneal has not presented clear and convincing evidence that the tablet of Example 11 would meet the 10 cP and 60 cP viscosity limitations. Maurin testified that if the tablet was dissolved in 10 milliliters of water, it would yield a solution much more viscous than 60 cP due to the presence of PEO. (Maurin Tr. 809-10.) Although Maurin's testimony certainly carries some intuitive appeal, the Court finds that it does not rise to the level of clear and convincing evidence of the '591 Application's anticipation of the '888 Patent's quantitative viscosity limitations.

Amneal tries to substantiate Maurin's predictions about the viscosity of Example 11's dosage forms by pointing to his viscosity tests of Concerta, a drug for the treatment of attention deficit hyperactive disorder. (*See* Sellers 2013 Tr. 94.) Concerta utilizes an osmotically controlled-release oral delivery system ("OROS"), the same type of drug delivery system disclosed in the '591 Application. (Maurin Tr. 772, 781-82.) Maurin tested the viscosity of several dosage strengths of Concerta after dissolving them in both 3 and 10 milliliters of water. (Maurin Tr. 796-804.) Each sample had a viscosity much greater than 60 cP. (Maurin Tr. 802, 806.) Although it is undisputed that Concerta and the '591 Application involve the same type of drug delivery system, the Court has

heard no evidence that Concerta actually practices the '591 Application. Moreover, Maurin did not record the shear rate he utilized in his viscosity tests, so the Court cannot determine whether his chosen shear rate falls within the '888 Patent's acceptable (albeit fairly large) range. For these reasons, the Court finds that Maurin's viscosity tests of Concerta do not show that the dosage forms of the '591 Application would satisfy the '888 Patent's 10 cP and 60 cP viscosity limitations.

2. Conclusions of Law

Based on the above findings of fact, the Court concludes that Amneal has not shown by clear and convincing evidence that the '963 Patent and the '591 Application disclose all the limitations of the asserted claims of the '888 Patent. Therefore, the Court concludes that the '888 Patent is not invalid for lack of novelty.

B. Obviousness Pursuant to 35 U.S.C. § 103

At trial, Amneal attempted to prove that the '888 Patent is invalid as obvious over the prior art. Purdue, meanwhile, introduced evidence on several objective indicia of nonobviousness. Because the claimed invention would have been obvious to persons of ordinary skill in the art as of August 2001, the Court concludes that the asserted claims of the '888 Patent are invalid pursuant to 35 U.S.C. § 103(a).

1. Findings of Fact

a) Level of Ordinary Skill in the Art

As noted above, for purposes of the asserted claims of the '888 Patent, a person of ordinary skill in the art has a degree in one or more fields of medicine, chemical engineering, chemistry, pharmaceutical science, polymer chemistry, pharmaceutics, pharmaceutical technology, pharmacokinetics, and/or pharmacology, and/or a number of years of industry training or experience in one or more of those fields. (Tr. 1033-34.)

In addition, the Court finds that as of the '888 Patent's priority date of August 2001, ordinarily skilled artisans understood how to adjust pharmaceutical formulations to provide the desired rate of release and level of therapeutic efficacy. (*See* Davies Tr. 1008-09.) They also knew how to determine the quantitative level of viscosity at which solutions become difficult to inject, which would have involved nothing more than conducting simple tests on the syringeability of viscosity standards. (Maurin Tr. 785.)

b) Scope and Content of the Prior Art[10]

(1) The prior art teaches that gelling agents reduce abuse potential.

Several prior art patents or patent applications teach that gelling agents reduce the abuse potential of pharmaceutical formulations. U.S. Patent No. 3,980,766 ("Shaw"), issued in 1976, is directed to oral dosage forms containing methadone, an API used for the treatment of narcotic drug addiction. (DTX 1492 at [45], 1:15-24.) Shaw discloses the addition of thickening agents to a dosage form, which "help[s] prevent injection abuse by increasing viscosity of a composition" such that "attempts at evaporation of an aqueous solution . . . will produce a highly viscous concentrate incapable of being handled by a syringe." (*Id.* at 1:65-2:2, 2:26-32.) Shaw states that when a tablet containing 40 milligrams of methadone was dispersed in 120 milliliters of water, filtered, and concentrated to 10 milliliters, "a viscous gummy mass resulted." (*Id.* at 6:3-21.) The concentrated solution could not be drawn into a syringe with a number 18 needle. (*Id.* at 6:21-23.) Shaw therefore teaches that thickening agents can prevent the syringeability of a solution that has been filtered and concentrated.

U.S. Patent No. 4,070,494 ("Hoffmeister"), issued in 1978, aims to reduce parenteral abuse of pharmaceutical compositions containing analgesics and other substances with abuse potential. (DTX 2170 at [45], 1:17-28.) Hoffmeister

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[10] Except where otherwise noted, the parties have stipulated that the references discussed in this section are prior art to the '888 Patent. (2014 Stip. ¶¶ 134-140.)

teaches a method of preventing aqueous extraction of the API through the use of a "nontoxic, aqueously gelable material" in a "quantity at least sufficient to form a gel with substantially no residual filterable liquid" when the dosage form is dissolved in water. (*Id.* at 2:3-8.) Hoffmeister therefore uses gelling agents to deter abuse by preventing extraction of the API and by reducing or eliminating the amount of solution that can be filtered for intravenous administration. (*See id.* at 1:66-2:6, 2:32-44.)

International Application No. WO 95/20947 ("Bastin"), published in 1995, attempts to remedy the perceived shortcomings of Hoffmeister, specifically the gelling agent's tendency to retard the release of the API. (DTX 1927 at (43), 1:22-29.) Bastin discloses a tablet in which the API and the gelling agent are separated into different layers in order to reduce their interaction. (*Id.* at 1:31-2:3.) Bastin further explains that the gelling agent has a viscosity in the range of 1,000 to 100,000 cP (*id.* at 3:24-26) and should be present in an amount "such that substantially no filterable material remains when the tablet is triturated with the minimal amount of aqueous medium needed to extract the drug" (*id.* at 4:6-10). Like Hoffmeister, then, Bastin relies on a gelling agent to prevent the extraction and filtration of drugs with abuse potential.

U.S. Patent Application Publication No. US 2002/0187192 ("Joshi"), filed in 2001, is titled "Pharmaceutical Composition Which Reduces or Eliminates Drug Abuse Potential."[11] (DTX 2611 at (54).) Joshi is directed at reducing the abuse potential of central nervous system stimulants such amphetamines. (*Id.* at [0008].) The application teaches that a "gel forming polymer reduces or

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[11] Although the parties did not stipulate that the Joshi publication qualifies as prior art to the '888 Patent, Purdue has never argued that it does not. Joshi was filed August 30, 2001 but claims priority to Provisional Application No. 60/287,509, filed April 30, 2001. With respect to the Court's obviousness analysis, the disclosures of the provisional application are identical to those of the non-provisional application. (*Compare* DTX 1497, *with* DTX 2611; *see also* Maurin Tr. 762-63). Therefore, Joshi qualifies as prior art to the '888 Patent. *See* 35 U.S.C. § 102(e) (2006); 35 U.S.C. § 119(e)(1) (2006); *see generally In re Giacomini*, 612 F.3d 1380 (Fed. Cir. 2010).

eliminates potential drug abuse by swelling in the presence of moisture which is, for example, present in the dermis layer of skin and mucous membrane, and thus, prevents nasal absorption and injectability of the drug." (*Id.* at [0009].) Joshi identifies PEO as a preferred gel forming polymer. (*Id.* at [0021].) It reports that "[g]el formation occurs" when a tablet containing PEO and a stimulant was crushed to form a powder, added to one milliliter of water, and stirred for one minute. (*Id.* at [0036], [0042].) The Examiner of the '888 Patent did not consider the Joshi publication. (Pls.' Responsive Post Trial Br., Dkt. No. 64, at 15 n. 10.)

(2) The prior art teaches that PEO functions as both a rate controlling agent and a gelling agent.

Several prior art references teach that PEO has rate controlling properties that may be employed in sustained release dosage forms. (*See* DTX 2013 at 0001; DTX 2361 at 8:52-9:4; PTX 1600 at 4:13-15; PTX 2359 at UT0001007.) For example, U.S. Patent No. 5,273,758 ("Royce"), issued in 1993, discloses that "polyethylene oxide has an adjustable rate control effect on the release of medicament from the dosage form, enabling in particular the preparation of sustained release dosage forms." (DTX 2344 at [57]; *see also id.* at [45], 2:43-48.) By 2001, PEO was also a known rate controlling agent in OROS formulations. (Oshlack Tr. 78-83.) In OROS systems, water enters the tablet and is absorbed by PEO; the swelling of the PEO causes the buildup of osmotic pressure, which pushes the API out through a hole in the tablet. (Maurin Tr. 772-73.) In addition, a 1999 dissertation by Zhang, one of the inventors of the '963 Patent, details how the molecular weight and amount of PEO influences the release profiles of various pharmaceutical formulations. (PTX 2359 at UT0001009-13.) The '591 Application goes a step beyond these references by explicitly disclosing controlled release dosage forms containing oxycodone in which PEO functions as a rate controlling agent. (DTX 9003 at 34:23-29, 37:1-6; Maurin Tr. 781-83.)

The gelling properties of PEO were also well-known in the art. An article published in 1958 in a scientific journal describes "the truly enormous thickening action of high molecular weight poly(ethylene oxide) in water." (DTX 9151A at 0008.) A photograph in the article depicts a thick, viscous PEO solution flowing slowly out of a jar, with a caption explaining that "[a] little Polyox resin goes a long way." (*Id.* at 0006.) In addition, the Royce patent explains that a one percent aqueous solution of 5-6 million molecular weight PEO has a viscosity of 7,200 to 10,000 cP. (DTX 2344 at 3:19-23.) And the Joshi publication, which is specifically directed toward abuse-resistant formulations, identifies polyethylene oxide as a preferred gel forming polymer. (DTX 2611 at 0021.) Notably, Benjamin Oshlack, one of the inventors of the '888 Patent, testified that he and his colleagues were aware that PEO had gelling properties even without conducting any testing. (Oshlack Tr. 75-76.)[12]

c) Differences Between the '888 Patent and the Prior Art

(1) The '888 Patent differs from the prior art by claiming oxycodone and requiring a quantitative level of viscosity.

The '888 Patent differs from the relevant prior art in a few key respects. First, the Court finds that the prior art does not explicitly teach that gelling agents prevent the abuse of oxycodone specifically. Shaw, Hoffmeister, Bastin, and Joshi (collectively, the "gelling patents") reference drugs such as methadone, analgesics, and central nervous system stimulants, but do not disclose oxycodone specifically. Importantly, however, these patents all involved APIs with abuse potential, and Hoffmeister notes that its gelling improvement "can be utilized with any medicinal agent which can be given orally but which has the potential for parenteral abuse." (DTX 2170 at 1:20-

[12] Although Amneal also argues that the gel-forming properties of Concerta (which contains PEO) were known among persons of skill in the art by August 2001, the Court cannot make that finding from the evidence in the record.

22.)[13] Consequently, although the '888 Patent differs from the prior art through its focus on oxycodone, the Court finds that this departure is not especially significant.

Second, the Court finds that, unlike the '888 Patent, the prior art does not disclose the quantitative level of viscosity that the gelling agent must produce. Even though several of the gelling patents described viscous solutions that could not be filtered or drawn into a syringe, none of them reported the quantitative viscosity (in centipoise) of those solutions.

(2) The '888 Patent does not represent a departure from the prior art in other significant ways.

At trial, Purdue presented evidence on three additional differences between the '888 Patent and the prior art that it contends are significant. The Court finds that these distinctions are either absent or overstated.

First, the Court cannot find that the prior art did not recognize PEO as a potential solution to the problems of drug abuse, as the '888 Patent does. Joshi lists PEO as a preferred gel forming polymer and explains that a tablet containing PEO formed a gel when mixed with water. (DTX 2611 at [0021], [0036], [0042].) Joshi is specifically directed toward abuse-resistant pharmaceutical formulations. (*Id.* at [0001].) Consequently, the '888 Patent is

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[13] Purdue also relies on a 2003 report by the College on Problems of Drug Dependence Taskforce to demonstrate that gelling was not considered a solution to the problem of OxyContin abuse. While the report does not constitute prior art to the '888 Patent, it is true that it does not discuss gelling. The article did note, however, that it may be possible to prevent abuse of OxyContin "by designing formulations that are less vulnerable to tampering." (PTX 2189 at 224.) In any event, the report has limited probative value in light of the lack of evidence that its authors qualify as persons of skill in the art for purposes of the '888 Patent.

not the first publication in the art to utilize PEO as a gelling agent in order to deter abuse.

Second, the Court rejects Purdue's argument that the '888 Patent departs from the prior art because it does not rely on filters. Shaw teaches that gelling agents prevent the syringing of solutions that have been filtered and concentrated; in other words, gelling apparently does not occur until after a filter has been employed. (*See* DTX 1492 at 6:20-24.) Filtration is not a necessary precursor to gel formation in the other gelling patents, however. Hoffmeister and Bastin added gelling agents to their dosage forms in order to produce solutions that were too viscous to pass through a filter. (*See* DTX 1927 at 4:6-10, 25:7-26:9; DTX 2170 at 2:9-17.) And Joshi does not discuss filters at all. (*See generally* DTX 2611.) Importantly, the dosage forms described in Hoffmeister, Bastin, and Joshi become viscous without the aid of a filter—just like the '888 Patent. The Court therefore finds that the '888 Patent's lack of reliance on filters does not separate it from the prior art in a meaningful way.

Finally, Purdue alleges that the prior art embraces the "conventional wisdom" that gelling agents are incompatible with controlled release formulations. (Davies Tr. 951-52.) Purdue relies on Bastin, one of the gelling patents, to support this argument. Bastin explains that combining an API and a gelling agent in the same layer "has the disadvantage that the gelling action is likely to retard the release of the drug in a manner similar to some known sustained release products which include water-swellable high molecular weight polymers to retard drug release." (DTX 1927 at 5:30-35.) Purdue argues that this disadvantage would have deterred persons of skill in the art from utilizing gelling agents in controlled release formulations. (*See* Davies Tr. 951-52.)

Placed in its proper context, Bastin provides very little support to Purdue. Bastin expressed concern about gelling agents' effect on drug release only with respect to *immediate release* formulations, for which delay poses a serious problem. (*See* DTX 1927 at 5:21-27; Davies Tr. 942.) By drawing an explicit comparison between gelling agents and the swelling properties of rate

controlling high molecular weight polymers[14] (DTX 1927 at 5:29-35), Bastin in fact implies that gelling agents are well-suited to controlled release dosage forms. And although all of the gelling patents focus primarily on immediate release tablets, Bastin notes that its invention may include a sustained release coating or "materials known in the art intended for the modification of release characteristics of the drug." (DTX 1927 at 5:1-3, 5:10-13.) Although the '888 Patent may be the first patent to disclose in detail controlled release dosage forms that utilize gelling agents to deter abuse, the Court cannot find that the prior art taught away from such formulations.

d) Objective Indicia of Nonobviousness

Purdue urges the Court to consider several objective indicia of nonobviousness, specifically commercial success, copying, long-felt but unmet need, skepticism, and industry acclaim.[15]

(1) There is insufficient evidence of the '888 Patent's commercial success.

The parties appear to agree that Reformulated OxyContin qualifies as a commercial success. (Hausman Tr. 282; Rao Tr. 660-61.) In 2009, Original OxyContin garnered net sales around $2.3 billion. (Rao Tr. 660.) After Reformulated OxyContin debuted in 2010, the opioid market in general began

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[14] Although Bastin does not expressly disclose PEO, the Court finds that persons of skill in the art would have immediately recognized PEO as a "water-swellable high molecular weight polymer[] to retard drug release." (DTX 1927 at 5:34-35; *see* Oshlack Tr. 81-82.)

[15] Purdue has also presented evidence on the "medical success" of Reformulated OxyContin in the form of epidemiological studies showing a decrease in OxyContin abuse. (*See generally* PTX 4225.) The Court declines to consider such evidence here because no court has ever deemed "medical success" to be an objective indication of nonobviousness. Rather, the relevant criterion appears to be "unexpected results." *See Power Integrations, Inc.*, 711 F.3d at 1368. The Court does not find that Reformulated OxyContin's success in reducing abuse was unexpected or surprising.

suffering from a secular decline. (*Id.* at 661.) Nonetheless, Reformulated OxyContin's sales have surpassed $1.8 billion dollars annually, qualifying it as a "blockbuster" drug in the pharmaceutical industry. (Hausman Tr. 282; Rao Tr. 660; Gasdia Tr. 217.) Reformulated OxyContin enjoys the highest net sales and is the most-prescribed branded extended release opioid on the market. (Gasdia Tr. 230; Hausman Tr. 282.)

The commercial success of Reformulated OxyContin, however, is meaningless unless it can be attributed to the claimed features of the '888 Patent. *See Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369-70 (Fed. Cir. 2011). The weight of the evidence presented at trial demonstrates that the required nexus is lacking. Prior to April 2013, Purdue did not market OxyContin on the basis of its abuse-deterrent properties. (Gasdia Tr. 234-36.) Even after that date, when the FDA permitted Purdue to describe these properties on the drug's label, Purdue's marketing message remained centered on the efficacy and side effect profile of Reformulated OxyContin. (*Id.* at 206.) And since the April 2013 label change, OxyContin's market share has not risen but instead has remained stable. (Hausman Tr. 283; *see also* Gasdia Tr. 230.) Hausman, Purdue's expert, admitted that as of July 2014 (the time of trial), it was too soon to tell whether or how the label change had affected sales. (Hausman Tr. 302.) Similarly, there is no data on whether the demand for OxyContin has increased or decreased as a result of its abuse-deterrent features. (*Id.* at 304-05.) Nor did Purdue raise the price of OxyContin to account for its new gelling properties. (*Id.* at 304.) This evidence strongly suggests that the commercial success of Reformulated OxyContin is not a result of the '888 Patent's claimed features but rather its bioequivalence to Original OxyContin. (*See* Rao Tr. 679.)

Purdue attempts to prove a nexus by linking commercial success to the FDA's April 2013 decision to prohibit generic versions of Original OxyContin, which was based partly on the new availability of abuse-deterrent Reformulated OxyContin. (*See* PTX 2157 at 7.) Hausman testified that but for the FDA's decision, sales of Reformulated OxyContin would have fallen by

approximately $500 million to $1.6 billion. (Hausman Tr. 275-76, 287-91.) This is because Reformulated OxyContin would have faced significant competition from generic versions of Original OxyContin. (*Id.* at 287.) Although Hausman's predictions as to the amount of lost sales are somewhat speculative, the Court credits his testimony that the current sales and market share of Reformulated OxyContin would be significantly lower if the FDA had not precluded generic competition on the basis of the product's abuse-deterrent features.

But even assuming the FDA decision supplies the required connection between the '888 Patent's gelling properties and the profitability of Reformulated OxyContin, the Court is not convinced that the '888 Patent itself can be considered a commercial success. Purdue concedes that if Reformulated OxyContin (which embodies the '888 Patent) had to compete with generic versions of Original OxyContin (which do not), Reformulated OxyContin would suffer significant declines in sales and market share. This indicates that physicians and patients either would not distinguish between Reformulated OxyContin and the generics or would not value the abuse-deterrent features of Reformulated OxyContin enough to pay a price premium. (*See* Rao Tr. 720-22.)

It is clear that the '888 Patent's gelling features allowed Purdue to achieve *regulatory* success in the form of the FDA decision, and that this regulatory success spared Purdue from facing generic competition and possibly a poor reception in the marketplace. But the Court is hesitant to equate regulatory success to commercial success when Purdue's own evidence shows that the '888 Patent would not be nearly as successful if consumers had the choice to reject Reformulated OxyContin in favor of a bioequivalent generic product not covered by the patent.

For these reasons, the Court finds that the evidence presented at trial is not sufficient to prove that the '888 Patent is a commercial success.

(2) Amneal's alleged copying of the invention is not an indication of nonobviousness.

Purdue has presented evidence to show that Amneal copied the gelling properties of the '888 Patent and Reformulated OxyContin. (*See, e.g.*, Davies Tr. 964.) The Court finds that this evidence does not serve as an indication of the patent's nonobviousness, as "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

(3) The '888 Patent did not fulfill a long-felt but unmet need.

The evidence does not support a finding that the '888 Patent fulfilled a long-felt but unmet need for abuse-resistant oxycodone dosage forms.[16] The public health crisis caused by oxycodone tampering and abuse began in early 2001, when the government and Purdue first acknowledged the problem. (*See* Sellers 2013 Tr. 82-83; PTX 2147; PTX 2148.) The inventors of the '888 Patent filed their provisional application that same year. ('888 Patent at (60).) The very short period of time that elapsed between the recognition of the need for abuse-deterrent oxycodone formulations and the invention that matured into the '888 Patent simply does not indicate any long-felt need. *See In re OxyContin Antitrust Litig.*, 994 F. Supp. 2d at 400-01, 428. Similarly, Purdue has presented no evidence that others tried but failed to develop abuse-resistant oxycodone products. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent*

[16] Purdue frames the issue too broadly by urging that an unmet need for "abuse-deterrent formulations" dates back at least to the 1970s, when the Shaw gelling patent was issued. But the '888 Patent's claims are directed at reducing the abuse potential of oxycodone alone ('888 Patent at 40:22-24), not at the abuse of drugs in general. The evidence in the record shows that the need for abuse-resistant formulations of oxycodone did not begin until 2001.

Litig., 676 F.3d 1063, 1082 (Fed. Cir. 2012) (noting that failure of others is closely related to long-felt need).

(4) Although Purdue received some acclaim for its invention, persons of skill in the art did not express skepticism.

The Court cannot find that persons of ordinary skill in the art expressed skepticism of the '888 Patent's invention. Although Purdue contends that there was concern that gelling agents could hinder the release of the API, that worry existed only with respect to immediate release dosage forms. *See supra*. The prior art, as discussed above, actually supported the idea that certain gelling agents were compatible with—and in fact advantageous to—controlled release formulations.

The Court finds, however, that the '888 Patent's inventors received some acclaim for their invention. By approving language on abuse deterrence for Reformulated OxyContin's label, the FDA recognized the formulation's gelling properties. (PTX 2158; Davies Tr. 964.) And in a letter to the FDA, the National Association of Attorneys General lauded the development of "tamper-resistant drugs" and expressed hope that "[a]dding new physical and chemical features to prescription opioids" would reduce abuse. (PTX 4237 at PRF0029508.) The Court finds that this evidence amounts to industry acclaim of the '888 Patent's gelling properties.

2. Conclusions of Law

a) It would have been obvious to respond to the oxycodone abuse crisis by creating a controlled release dosage form that utilizes PEO as a gelling and rate control agent.

Based on the findings of fact set forth above, the Court concludes that the claimed invention of the '888 Patent would have been obvious to persons of ordinary skill in the art as of August 2001. First, the OxyContin abuse crisis—

which was publicly known by early 2001—provided motivation to produce an abuse-deterrent oxycodone formulation. In particular, persons of skill in the art would have been motivated to invent controlled release oxycodone tablets that resist injection, snorting, and oral ingestion, the known methods of abuse. (PTX 2147 at PRF0022156; *see* Sellers 2013 Tr. 99.)

To fulfill this goal, persons of ordinary skill in the art would have turned first to prior art that addresses abuse-deterrent formulations. Viewed together, Shaw, Hoffmeister, Bastin, and Joshi teach that gelling agents frustrate the extraction and injection of dissolved dosage forms. And Joshi—which was not before the Examiner of the '888 Patent—specifically identifies PEO as a preferred gelling agent in abuse-resistant tablets. (DTX 2611 at [0021].) These references would have given an ordinarily skilled artisan motivation to incorporate a gelling agent, and more specifically PEO, into an oxycodone dosage form.

Moreover, the prior art confirmed that PEO was entirely compatible in controlled release formulations. Indeed, persons of skill in the art would have recognized PEO as an ideal component of an abuse-deterrent controlled release tablet in light of PEO's gelling and rate controlling properties, both of which had long been known in the art. Bastin, in fact, discloses that high molecular weight polymers such as PEO function as both gelling and rate control agents. *See supra*.

Moreover, the McGinity and Zhang Application and the '591 Application provided a strong starting point for producing a gel-forming, controlled release oxycodone dosage form. Although these references are not directed toward the reduction of abuse potential, they relate to the field of the endeavor because they provide detailed information on PEO-based controlled release dosage forms. *See In Re ICON*, 496 F.3d at 1379-80. In fact, the inventors relied on prior art concerning OROS dosage forms, which are covered by the '591 Application, in the '888 Patent. ('888 Patent at 22:50-25:37; Oshlack Tr. 78, 83.) Upon reading either the '591 Application or the McGinity and Zhang Application, ordinarily skilled artisans would have immediately suspected

that the disclosed dosage forms would produce extremely viscous solutions due to the presence of high molecular weight PEO.[17] (Muzzio Tr. 506; Maurin Tr. 748, 786-87.) They would also have had a strong expectation of success in incorporating oxycodone into these dosage forms (*see* Maurin Tr. 867-69), which the '591 Application expressly discloses.

Finally, it was well within the level of skill in the art to design an abuse-resistant oxycodone dosage form to achieve a therapeutic effect lasting at least about twelve hours. The '591 Application explains that its dosage forms "provide a therapeutically effective blood level of the medicament for 30 minutes to 24 hours." (DTX 9003 at 5:4-6.) Persons of skill in the art could also have looked to Original OxyContin and its associated patents for guidance, since that drug produced at least twelve hours of therapeutic efficacy. (*See* Davies Tr. 1007.) The evidence adduced at trial does not show that ordinarily skilled artisans would have feared that including PEO or oxycodone in the dosage form would have posed a significant obstacle to obtaining the desired therapeutic effect. (*See* Davies 1007-13; Maurin Tr. 748-51, 811-12.) The Court therefore concludes that an ordinarily skilled artisan would have had a reasonable expectation of success in attaining a 12-hour therapeutic effect from a controlled release, PEO-based oxycodone dosage form.

In sum, although no single prior art reference discloses an abuse-deterrent controlled release oxycodone dosage form containing the gelling agent PEO, persons of skill in the art would have been motivated to combine the teachings of the prior art to arrive at such an invention and would have had a reasonable—indeed, a strong—expectation of success in doing so. *See OSRAM Sylvania, Inc.*, 701 F.3d at 706; *see also KSR*, 550 U.S. at 418 (noting that the

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[17] The fact that Amneal did not prove by clear and convincing evidence that the '591 Application inherently discloses very viscous dosage forms does not vitiate the reference's relevance to the obviousness analysis. The Court is satisfied that an ordinarily skilled artisan reading the '591 Application (and the '963 Patent) would suspect that its tablets form gels and undertake further study to confirm that hypothesis.

obviousness analysis may "take account of the inferences and creative steps that a person of ordinary skill in the art would employ").

b) The remaining features of the claimed invention are obvious.

The Court concludes that the remaining features of the claimed invention, specifically the patent's quantitative viscosity and tampering limitations, are also obvious. First, it would have required very little effort for persons of skill in the art to determine the quantitative level of viscosity at which syringing and injection became difficult. Arriving at the 10 cP and 60 cP viscosity limitations would have involved nothing more than simple experimentation of the syringeability of viscosity standards. (Maurin Tr. 784-85.) Consequently, although the '888 Patent was the first to specify numerical viscosity requirements for abuse-resistant dosage forms, that feature does not represent a nonobvious advancement over the prior art. *Cf. Abbott Labs. v. Sandoz*, 544 F.3d 1341, 1379 (Fed. Cir. 2008).

Second, the patent's tampering limitations, which provide that the requisite viscosity results when the dosage form is tampered and dissolved in a small amount of aqueous liquid ('888 Patent at 40:25-29, 42:10-17), are also obvious. Persons of ordinary skill in the art would have known, as a result of their training and experience, that tablets containing PEO would form a gel with a viscosity of at least about 10 cP or 60 cP when crushed and dissolved in less than 10 milliliters of water or other aqueous liquid. (*See* Maurin Tr. 813.) And they would have known that using heated dissolution would result in even higher viscosity values. (*See* Davies Tr. 923.) The '888 Patent's tampering limitations, therefore, would have been obvious at the time of the invention.

c) All asserted claims of the '888 Patent are invalid as obvious.

In conclusion, the Court finds by clear and convincing evidence that all asserted claims of the '888 Patent are invalid as obvious. Viewed in light of the level of skill in the art and the extensive body of relevant prior art references,

the '888 Patent essentially embodies the "predictable result[]" of the "combination of familiar elements according to known methods." *KSR*, 550 U.S. at 398. Having considered the objective indicia of nonobviousness and found sufficient evidence of only one criterion, industry acclaim, the Court is satisfied that hindsight has not influenced its obviousness analysis. Consequently, because the invention is obvious, the asserted claims of the '888 Patent are invalid pursuant to 35 U.S.C. § 103(a).

C. Indefiniteness Pursuant to 35 U.S.C. § 112

At trial, Amneal attempted to prove that the '888 Patent's lack of specific guidance on shear rate, tampering and testing temperature, and extent of dissolution renders its viscosity test indefinite. The Court concludes that Amneal has met its burden of proof only with respect to claim 7.

1. Findings of Fact

a) Shear Rate

In its claim construction *supra*, the Court determined that although the '888 Patent's viscosity test allows a shear rate range of at least .01 to 100 reciprocal seconds, the patent does not identify specific upper and lower limits for that range. Amneal contends that this deficiency is fatal to the asserted claims of the patent.

(1) Shear rate determines whether some accused products meet claim 5's 60 cP viscosity limitation.

The viscosity testing that Davies conducted on the 30 milligram tablets produced by Teva (Amneal's co-defendant at trial) demonstrates that infringement, at least in some cases, depends on shear rate. Davies utilized the same testing protocol that he used for Amneal's tablets, which the Court described in detail in its findings on infringement. (Davies Tr. 348-60.) When tampered and tested at 25° C., all dosage strengths of Teva's proposed tablets

had viscosities above 10 cP at shear rates ranging between .01 and 100 reciprocal seconds. (Davies Tr. 368-69; PTX 4204.) Teva's 30 milligram tablet, however, began to fall below 60 cP at shear rates above 25 reciprocal seconds, dropping to 50.1 cP at a shear rate of 100 reciprocal seconds. (DTX 9179 at 0097; Davies Tr. 415-16; PTX 4204 at CATTEV0000276.) The Court finds by clear and convincing evidence that the choice of shear rate—specifically, whether to test above or below 25 reciprocal seconds, which is within the range of shear rates the patent allows—determines whether Teva's 30 milligram tablet meets the 60 cP viscosity limitation of claim 5.

Moreover, the viscosity of all of Teva's dosage strengths fell as shear rate approached 100 reciprocal seconds, indicating that viscosity would continue to decline. (PTX 4204.) The Court credits Muzzio's testimony that at least some of Teva's tablets would have fallen below 60 cP at shear rates slightly above 100 reciprocal seconds, had Davies continued testing them. (Muzzio Tr. 526.) Davies himself admitted that at a shear rate of 100 reciprocal seconds, the viscosity of all of Teva's tablets had not yet reached region III of the pseudo-plastic viscosity curve described in Schramm. (Davies Tr. 973; *see also* PTX 4204 at CATTEV0000278-79.) Amneal's tablets exhibited the same pattern. (*See generally* PTX 4198.) The Court finds by clear and convincing evidence that the viscosity of Amneal's tablets would have continued to decline at shear rates above 100 reciprocal seconds before finally leveling out. (PTX 4232 at PRF0029329-30; *see* Davies Tr. 973-74.)

(2) Specifying shear rate is standard practice among ordinarily skilled artisans.

The Court also finds that specifying shear rate is standard practice among ordinary skilled artisans. The scientific literature utilized by persons of skill in the art highlights the importance of identifying shear rate or information from which shear rate may be determined (*i.e.*, rheometer model, cup size, spindle size, and test speed). The manual for the instrument that the '888 Patent's inventors used for Example 3 states that "[a] repeatable viscosity test should control or specify . . . shear rate." (DTX 9173 at 0021.) The brochure for PolyOx,

Dow's brand of polyethylene oxide, reports the viscosity of different grades of polyethylene oxide along with the viscometer model, spindle size, and test speed. (DTX 9117 at 0018.) Similarly, the '060 Patent—which Purdue asserted against Teva during trial—links the viscosity of PEO and other polymers to a specific viscometer model, spindle size, and test speed. (PTX 4000 at 6:2-9.) A patent to Royce includes the same information when reporting the viscosity of certain grades of PolyOx. (DTX 2344 at 3:14-23.) Although these latter three references omit cup size, only one cup size (a 600 milliliter beaker) may be used with the particular viscometer at issue. (DTX 9173 at 0027; Muzzio Tr. 651-53.)

Purdue attempts to downplay the significance of these references by pointing to other instances in which shear rate was not specified. First, Amneal utilized as a trial exhibit a website printout listing the approximate viscosities of common household items such as milk, motor oil, honey, and mustard. (DTX 9146.) The fact that this list does not identify shear rate proves nothing, as it clearly functions as an illustration of viscosity for the casual reader and not as an authoritative reference for the ordinarily skilled artisan. (Muzzio Tr. 620-22.) Second, Purdue points out that Maurin did not record shear rate in his viscosity tests of Concerta. (Maurin Tr. 886.) Although this observation carries some weight, it is not enough to alter the Court's finding, by clear and convincing evidence, that specifying shear rate in viscosity testing represents standard practice among persons of ordinary skill in the art—even if the occasional artisan fails to live up to that standard.

b) Tampering and Testing Temperature

Amneal also contends that the '888 Patent is indefinite for failing to provide specific guidance on the range of acceptable tampering and testing temperatures. It is essentially undisputed that tampering and testing temperature affect viscosity. (Muzzio Tr. 527; Davies Tr. 982.) The Court finds, however, that Amneal has not shown by clear and convincing evidence that the choice of tampering or testing temperature influences whether or not an accused product infringes the '888 Patent.

To support Amneal's indefiniteness argument, Muzzio prepared tablets of different weights containing CPM, PEO, and magnesium stearate. (Muzzio Tr. 530; DTX 9111 at 0003.) He ground the tablets, added 10 milliliters of water to each, placed them on a shaker table until they had dissolved, and then measured the viscosity of the solutions using a standard rheometer. (Muzzio Tr. 530; DTX 9111 at 0007.) Muzzio tested the tablets at 20°, 30°, 40°, 50°, and 60° C. (Muzzio Tr. 527), temperatures that are significantly lower than boiling and therefore represent reasonable choices. He used two different shear rates: 30 and 85 reciprocal seconds, which are also within the patent's permissible range. (DTX 9113 at 0003.) Muzzio's results show that the choice of testing temperature determines whether the tablets met the patent's 10 cP and 60 cP viscosity limitations. (DTX 9113 at 0003; Muzzio Tr. 530-31.) One of his formulations had a viscosity above 10 cP at both 20° and 30° C., but fell below 10 cP when tested at 40°, 50°, and 60° C. (DTX 9113 at 0003.) Another formulation attained a viscosity above 60 cP at 20°, but dropped below that level at 30°, 40°, 50°, and 60° C. (*Id.*)

The Court gives only modest weight to Muzzio's viscosity tests because his tablets do not meet all the limitations of the '888 Patent. First, because his laboratory did not have a federal license to use oxycodone, Muzzio substituted CPM. (Muzzio Tr. 501.) Second, Muzzio's tablets do not appear to be controlled release dosage forms that provide a therapeutic effect for at least about 12 hours. Nonetheless, the Court has not been presented with convincing evidence that Muzzio would have obtained different viscosity results if his tablets had featured oxycodone instead of CPM, possessed controlled release properties, and provided a 12-hour therapeutic effect. Although Muzzio's tablets do not embody certain aspects of the '888 Patent, the Court accords his tests some weight on the basis that the differences may not be critical.

To further support its argument that tampering and testing temperature constitute outcome-determinative factors, Amneal contrasts the viscosity tests of Reformulated OxyContin conducted by Purdue scientists with those conducted by Davies. Davies found that temperature did not influence

whether Reformulated OxyContin satisfied the '888 Patent's viscosity limitations. Using the same testing protocol described in the Court's findings on infringement, Davies tampered all dosage strengths of Reformulated OxyContin at both 25° C. and 50° C.; he then measured viscosity at 25° C. (Davies Tr. 348-59.) The samples tampered at 50° C. were more viscous than those tampered at 25° C., but the viscosity of all tablets was above 60 cP. (Davies Tr. 366-67.) In other words, Davies found that varying tampering temperature (while keeping testing temperature constant) did not affect whether Reformulated OxyContin met the '888 Patent's quantitative viscosity limitations.

At first glance, Purdue's viscosity tests appear to contradict Davies's findings. Purdue measured the viscosity of 80 milligram Reformulated OxyContin tablets that had been dissolved in 10 milliliters of boiling water. (DTX 9169 at 0037, 0070; Davies Tr. 984.) Purdue then tested the viscosity of these solutions at both 95° and 37° C. (DTX 9169 at 0070-71.) At some shear rates, the viscosity of the solutions tested at both temperatures was less than 60 cP, although viscosity never dropped below 10 cP. (*Id.*; *see also* Davies Tr. 985.) According to Amneal, Purdue's tests prove that tampering and testing temperature directly influence whether an accused product infringes the '888 Patent.

The Court does not assign any weight to Purdue's viscosity tests for two reasons. First, the tests that Purdue conducted at 95° C. are not probative of the validity of the '888 Patent because persons of skill in the art would not utilize that testing temperature. *See supra*. Second, the results that Purdue obtained for the tablets tested at 37° C. are largely a function of shear stress rather than tampering or testing temperature. At shear rates of 40, 63, and 100 reciprocal seconds,[18] one sample attained viscosities between 53 and 56 cP. (DTX 9169 at 0071.) Yet the viscosity of a second sample tested at those exact same shear rates was significantly higher, in the range of 531 to 825 cP. (*Id.*) While Purdue

[18] The Court has rounded these figures to the nearest whole number.

tested the first sample at shear stresses between 2.23 to 5.61 Pascals, shear stress for the second sample ranged from 32.8 to 53.1 Pascals. (*Id.*) Although the parties did not focus on the concept of shear stress at trial, it is clear that shear stress—rather than tampering or testing temperature—likely caused the discrepancy between the two samples. The Court therefore assigns no weight to Purdue's test results for the purpose of indefiniteness.

With Purdue's viscosity tests out of the picture, the only evidence suggesting that tampering and testing temperature are outcome-determinative factors consists of Muzzio's tests of his CPM tablets. Because those tablets do not satisfy all the limitations of claim 1, the Court concludes that Muzzio's test results do not rise to the level of clear and convincing evidence that temperature determines whether an accused product achieves a viscosity of 10 cP or 60 cP.

c) Extent of Dissolution

Finally, Amneal argues that the '888 Patent is indefinite because viscosity fluctuates based on the extent to which the dosage form has dissolved. The Court has already determined that the patent's viscosity test requires persons of skill in the art to visually inspect the sample to confirm that the soluble components of the dosage form have dissolved. Amneal has not shown by clear and convincing evidence that ordinarily skilled artisans cannot successfully carry out this inspection. Although the solutions contemplated by the patent may be opaque or cloudy, Davies, Muzzio, and Maurin were all able to determine the point at which the dosage form had adequately dissolved and was ready for viscosity testing. (Davies Tr. 353, 925; Muzzio Tr. 603; Maurin Tr. 798.) Nor is there any evidence that this determination is completely dependent on an individual's subjective opinion. *See Halliburton*, 514 F.3d at 1249. Accordingly, the Court finds by clear and convincing evidence that the extent of dissolution neither determines infringement nor requires an assessment that an ordinarily skilled artisan simply cannot make.

2. Conclusions of Law

The Court concludes that the '888 Patent's failure to provide sufficient guidance on shear rate renders claim 7 indefinite. As the Court has construed it, the patent's viscosity test permits, at a minimum, shear rates ranging from .01 to 100 reciprocal seconds. Yet even within this range, the choice of shear rate determines whether Teva's 30 milligram tablet satisfy claim 7's viscosity limitation of 60 cP. *See supra*. In other words, shear rate directly impacts the results of the viscosity test and therefore the determination of infringement, yet the patent does not tell an ordinarily skilled artisan how to select shear rate. There is hardly a better example of indefiniteness. *See, e.g., Frans Nooren Afdichtingssystemen B.V.*, 744 F.3d at 724; *see also In re OxyContin Antitrust Litig.*, 994 F. Supp. 2d at 433-34. The Court concludes by clear and convincing evidence that the viscosity test, as expressed in claim 7, "fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus*, 134 S. Ct. at 2124.

The patent's shortcomings regarding shear rate do not automatically invalidate the remaining asserted claims, however. Claim 5 only requires a viscosity of 10 cP, and Amneal has not shown that the choice of shear rate impacts whether an accused product meets this limitation. Consequently, even though persons of skill in the art could reasonably choose different shear rates when conducting the viscosity test, they would still be able to ascertain the scope of claim 5. Likewise, claims 23 and 24, which are multiple dependent claims, are only indefinite with respect to shear rate when they depend from claim 7 and therefore incorporate the 60 cP viscosity limitation. When claims 23 and 24 depend from claims 2, 3, 5, or 6, the dosage form need only achieve a viscosity of 10 cP, and the choice of shear rate does not affect that limitation.[19]

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[19] The Court declines Amneal's invitation to speculate about the viscosities that would result from shear rates up to 200,000 reciprocal seconds, which Muzzio testified might be encountered in a syringe. (Muzzio Tr. 518.) First, no expert at trial utilized such extreme shear rates in their tests. Second, the Schramm reference suggests that at very

Similarly, the Court cannot conclude by clear and convincing evidence that any of the asserted claims are indefinite with respect to tampering temperature, testing temperature, or extent of dissolution. Even though the '888 Patent does not set forth precise guidance on these testing variables, Amneal has not proven that the uncertainty is severe enough to make the viscosity test indefinite. Specifically, Amneal has not shown that these variables impact whether an accused product infringes the patent; rather, the evidence shows that even when persons of skill in the art fill the gaps in different ways, their choices do not produce conflicting results on infringement. *See Nautilus*, 134 S. Ct. at 2128 (suggesting that a claim is not ambiguous merely because readers "could reasonably interpret the claim's scope differently"). The Court concludes that despite the patent's lack of specific direction on tampering temperature, testing temperature, and extent of dissolution, persons of ordinary skill in the art can still discern, with reasonable certainty, the scope of the invention.

In conclusion, the Court finds by clear and convincing evidence that the patent's insufficient guidance on shear rate renders claim 7 of the '888 Patent indefinite pursuant to 35 U.S.C. § 112.

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high shear rates above 100 reciprocal seconds or so, viscosity is largely independent of shear rate. (*See* PTX 4232 at PRF00229329.) Therefore, the Court cannot find that viscosity at 200,000 reciprocal seconds would differ from viscosity at 100 reciprocal seconds in a manner that renders the 10 cP limitation indefinite.

PART 3. CONCLUSION AND RELIEF

The Court has found by a preponderance of the evidence that Amneal infringes the asserted claims of the '888 Patent. However, the Court also concludes that Amneal escapes liability for that infringement because it has shown by clear and convincing evidence that the '888 patent is invalid. Specifically, all of the asserted claims are invalid for obviousness, while clam 7 is also invalid for indefiniteness.

Based on the findings of fact and conclusions of law articulated above, the Court hereby ORDERS the following:

1. Plaintiffs' requests for relief are denied.
2. The following declaratory judgment shall enter in favor of Amneal Pharmaceuticals, LLC, and against plaintiffs Purdue Pharma L.P., The P.F. Laboratories, Inc., and Purdue Pharmaceuticals L.P.: Claims 5, 7, 23, and 24 of U.S. Patent No. 8,337,888 are invalid.
3. Amneal's counterclaim for declaratory judgment of non-infringement of claims 5, 7, 23, and 24 of U.S. Patent No. 8,337,888 is denied.
4. No attorney's fees will be awarded because the prevailing party, Amneal Pharmaceuticals, LLC, has not demonstrated that this is an exceptional case.

Dated: New York, New York
April 8, 2015

SO ORDERED:

Sidney H. Stein, U.S.D.J.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

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In re: OXYCONTIN ANTITRUST LITIGATION

04 **MD** 1603 (SHS)

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PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC. and PURDUE PHARMACEUTICALS L.P.,

Plaintiffs,

13 **CIVIL** 3372 (SHS)

-against-

JUDGMENT

AMNEAL PHARMACEUTICALS, USA, INC.,

Defendant.

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Whereas this Court having held a bench trial concerning the infringement and validity of the United States Patent No. 8,337,888 ("the '888 Patent") , which is associated with the opioid pain reliever OxyContin, and the matter having come before the Honorable Sidney H. Stein, United States District Judge, and the Court, on April 8, 2015, having rendered its Findings of Fact and Conclusions of Law ordering the following: 1. Plaintiffs' requests for relief is denied; 2. The following declaratory judgment shall enter in favor of Amneal Pharmaceuticals, LLC, and against plaintiffs Purdue Pharma L.P., The P.F. Laboratories, Inc., and Purdue Pharmaceuticals L.P.: Claims 5,7.23, and 24 of U.S. Patent No. 8,337,888 are invalid; 3. Amneal's counterclaim for declaratory judgment for non-infringement of claims 5,7,23, and 24 of U.S. Patent No. 8,337,888 is denied; 4, No attorneys fees will be awarded, because the prevailing party, Amneal Pharmaceuticals, LLC, has not demonstrated that this is an exceptional case, it is,

ORDERED, ADJUDGED AND DECREED: That for the reasons stated in the Court's Findings of Fact and Conclusions of Law, the Court Orders as follows:

1. Plaintiffs' requests for relief is denied.

2. The following declaratory judgment is entered in favor of Amneal Pharmaceuticals, LLC, and against plaintiffs Purdue Pharma L.P., The P.F. Laboratories, Inc., and Purdue Pharmaceuticals L.P.: Claims 5,7,23, and 24 of U.S. Patent No. 8,337,888 are invalid.

3. Amneal's counterclaim for declaratory judgment of non-infringement of claims 5,7,23, and 24 of U.S. Patent No. 8,337,888 is denied.

4. No attorneys fees will be awarded, because the prevailing party, Amneal Pharmaceuticals, LLC, has not demonstrated that this is an exceptional case.

Dated: New York, New York
April 9, 2014

RUBY J. KRAJICK

Clerk of Court

BY: _____

Deputy Clerk

THIS DOCUMENT WAS ENTERED ON THE DOCKET ON _____

US008337888B2

(12) **United States Patent**
Wright et al.

(10) **Patent No.: US 8,337,888 B2**
(45) **Date of Patent: *Dec. 25, 2012**

(54) **PHARMACEUTICAL FORMULATION CONTAINING GELLING AGENT**

(75) Inventors: **Curtis Wright**, Norwalk, CT (US); **Benjamin Oshlack**, New York, NY (US); **Christopher Breder**, Greenwich, CT (US)

(73) Assignee: **Purdue Pharma L.P.**, Stamford, CT (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/349,449**

(22) Filed: **Jan. 12, 2012**

(65) **Prior Publication Data**

US 2012/0108622 A1 May 3, 2012

Related U.S. Application Data

(63) Continuation of application No. 12/653,115, filed on Dec. 8, 2009, now abandoned, which is a continuation of application No. 10/214,412, filed on Aug. 6, 2002, now abandoned.

(60) Provisional application No. 60/310,534, filed on Aug. 6, 2001.

(51) **Int. Cl.**
A61K 9/20 (2006.01)

(52) **U.S. Cl.** **424/464**; 424/465

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed in certain embodiments is a controlled release oral dosage form comprising a therapeutically effective amount of a drug susceptible to abuse together with one or more pharmaceutically acceptable excipients; the dosage form further including a gelling agent in an effective amount to impart a viscosity unsuitable for administration selected from the group consisting of parenteral and nasal administration to a solubilized mixture formed when the dosage form is crushed and mixed with from about 0.5 to about 10 ml of an aqueous liquid; the dosage form providing a therapeutic effect for at least about 12 hours when orally administered to a human patient.

24 Claims, No Drawings

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PHARMACEUTICAL FORMULATION CONTAINING GELLING AGENT

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 12/653,115, filed Dec. 8, 2009, which is a continuation of U.S. patent application Ser. No. 10/214,412, filed Aug. 6, 2002, which claims the benefit of U.S. Provisional Application No. 60/310,534, filed Aug. 6, 2001. The contents of these applications are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Opioid analgesics are sometimes the subject of abuse. Typically, a particular dose of an opioid analgesic is more potent when administered parenterally as compared to the same dose administered orally. Therefore, one popular mode of abuse of oral opioid formulations involves the extraction of the opioid from the dosage form, and the subsequent injection of the opioid (using any "suitable" vehicle for injection) in order to achieve a "high." Also, some formulations can be tampered with in order to provide the opioid agonist contained therein better available for illicit use. For example, a controlled release opioid agonist formulation can be crushed in order to provide the opioid contained therein available for immediate release upon oral or nasal administration. An opioid formulation can also be abusable by administration of more than the prescribed dose of the drug.

Opioid antagonists have been combined with certain opioid agonists in order to deter the parenteral abuse of opioid agonists. In the prior art, the combination of immediate release pentazocine and naloxone has been utilized in tablets available in the United States, commercially available as Talwin®Nx from Sanofi-Winthrop. Talwin®Nx contains immediate release pentazocine hydrochloride equivalent to 50 mg base and naloxone hydrochloride equivalent to 0.5 mg base. A fixed combination therapy comprising tilidine (50 mg) and naloxone (4 mg) has been available in Germany for the management of pain since 1978 (Valoron®N, Goedecke). A fixed combination of buprenorphine and naloxone was introduced in 1991 in New Zealand (Temgesic®Nx, Reckitt & Colman) for the treatment of pain.

Purdue Pharma EP currently markets sustained-release oxycodone in dosage forms containing 10, 20, 40, and 80 mg oxycodone hydrochloride under the tradename OxyContin.

U.S. Pat. Nos. 5,266,331; 5,508,042; 5,549,912 and 5,656,295 disclose sustained release oxycodone formulations.

U.S. Pat. Nos. 4,769,372 and 4,785,000 to Kreek describe methods of treating patients suffering from chronic pain or chronic cough without provoking intestinal dysmotility by administering 1 to 2 dosage units comprising from about 1.5 to about 100 mg of opioid analgesic or antitussive and from about 1 to about 18 mg of an opioid antagonist having little to no systemic antagonist activity when administered orally, from 1 to 5 times daily.

U.S. Pat. No. 6,228,863 to Palermo et al. describes compositions and methods of preventing abuse of opioid dosage forms.

WO 99/32119 to Kaiko et al. describes compositions and methods of preventing abuse of opioid dosage forms.

U.S. Pat. No. 5,472,943 to Crain et al. describes methods of enhancing the analgesic potency of bimodally acting opioid agonists by administering the agonist with an opioid antagonist.

U.S. Pat. No. 3,980,766 to Shaw et al., is related to drugs which are suitable for therapy in the treatment of narcotic drug addiction by oral use, e.g., methadone, formulated to prevent injection abuse through concentration of the active component in aqueous solution by incorporating in a solid dosage or tablet torr of such drug an ingestible solid having thickening properties which cause rapid increase in viscosity upon concentration of an aqueous solution thereof.

However, there still exists a need for a safe and effective treatment of pain with opioid analgesic dosage forms which are less subject to abuse than current therapies.

All documents cited herein, including the foregoing, art incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less parenteral abuse than other dosage forms.

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less intranasal abuse than other dosage forms.

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less oral abuse than other dosage forms.

It is a further object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less diversion than other dosage forms.

It is a further object of certain embodiments of the invention to provide a method of treating pain in human patients with an oral dosage form of an opioid analgesic while reducing the abuse potential of the dosage form.

It is a further object of certain embodiments of the invention to provide a method of manufacturing an oral dosage form of an opioid analgesic such that it has less abuse potential.

These objects and others are achieved by the present invention, which is directed in part to an oral dosage form comprising an opioid analgesic; and at least one aversive agent for reducing the abuse of the opioid analgesic.

In certain embodiments of the present invention, the oral dosage forms of the present invention comprising an opioid analgesic; and an aversive agent or agents as a component(s) of the dosage form helps to prevent injection, inhalation, and/or oral abuse by decreasing the "attractiveness" of the dosage form to a potential abuser.

In certain embodiments of the present invention, the dosage form comprises an aversive agent such as a bittering agent to discourage an abuser from tampering with the dosage form and thereafter inhaling or swallowing the tampered dosage form. Preferably, the bittering agent is released when the dosage form is tampered with and provides an unpleasant taste to the abuser upon inhalation and/or swallowing of the tampered dosage form.

In certain embodiments of the present invention, the dosage form comprises an aversive agent such as an irritant to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, or swallowing the tampered dosage form. Preferably, the irritant is released when the dosage form is tampered with and provides a burning or irritating effect to the abuser upon inhalation, injection, and/or swallowing of the tampered dosage form.

In certain embodiments of the present invention, the dosage form comprises an aversive agent such as a gelling agent to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, and/or swallowing the tam-

pered dosage form. Preferably, the gelling agent is released when the dosage form is tampered with and provides a gel-like quality to the tampered dosage form which slows the absorption of the opioid analgesic such that an abuser is less likely to obtain a rapid "high". In certain preferred embodiments, when the dosage form is tampered with and exposed to a small amount (e.g., less than about 10 ml) of an aqueous liquid (e.g., water), the dosage form will be unsuitable for injection and/or inhalation. Upon the addition of the aqueous liquid, the tampered dosage form preferably becomes thick and viscous, rendering it unsuitable for injection. The term "unsuitable for injection" is defined for purposes of the present invention to mean that one would have substantial difficulty injecting the dosage form (e.g., due to pain upon administration or difficulty pushing the dosage form through a syringe) due to the viscosity imparted on the dosage form, thereby reducing the potential for abuse of the opioid analgesic in the dosage form. In certain embodiments, the gelling agent is present in such an amount in the dosage form that attempts at evaporation (by the application of heat) to an aqueous mixture of the dosage form in an effort to produce a higher concentration of the therapeutic agent, produces a highly viscous substance unsuitable for injection.

When nasally inhaling the tampered dosage form, the gelling agent can become gel like upon administration to the nasal passages due to the moisture of the mucous membranes. This also makes such formulations aversive to nasal administration, as the gel will stick to the nasal passage and minimize absorption of the abusable substance. In certain embodiments of the present invention, the dosage form comprises a combination of any or all of the aforementioned aversive agents (e.g., a bittering agent, an irritant, and/or a gelling agent) to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, and/or swallowing the tampered dosage form.

Embodiments specifically contemplated include bittering agent; gelling agent; irritant; bittering agent and gelling agent; bittering agent and irritant; gelling agent and irritant; and bittering agent and gelling agent and irritant.

In certain preferred embodiments, the dosage forms are controlled release oral dosage forms comprising a therapeutically effective amount of an opioid analgesic with one or more of the aversive agents described above such that the dosage form provides effective pain relief for at least about 12 hours, or at least about 24 hours when orally administered to a human patient.

In certain embodiments of the present invention the aversive agent present in the dosage form is present in a substantially non-releasable form (i.e., "sequestered") when the dosage form is administered intact as directed. Preferably, because the aversive agent is present in the dosage form in a substantially non-releasable form, it is not substantially released in the gastrointestinal tract when the dosage form is orally administered intact.

In other embodiments, the aversive agent may not be "sequestered" as disclosed above wherein the aversive agent is not released or minimally released from an intact dosage form, but may have a modified or sustained release so as not to dump the aversive agent in a particular section of the gastrointestinal tract, e.g. the stomach, where it may cause an unwanted effect such as excessive irritation. The aversive agent can be combined with an enteric carrier to delay its release or combined with a carrier to provide a sustained release of the aversive agent. However, it is contemplated in the present invention that the aversive agent will preferably not have any significant side effect (e.g., gastrointestinal side effect) even if all of the aversive agent is immediately released upon oral administration of an intact dosage form as directed.

The aversive agent(s) can also be in the dosage form in releasable form and non-releasable form in any combination. For example, a dosage form can have a bittering agent, irritant, gel or combination thereof in releasable form and non-releasable form as disclosed in U.S. Application entitled "Pharmaceutical Formulations Containing Opioid Agonist, Releasable Antagonist, and Sequestered Antagonist" filed Aug. 6, 2002, the disclosure of which is hereby incorporated by reference in its entirety.

The term "aversive agent" is defined for purposes of the present invention to mean a bittering agent, an irritant, a gelling agent, or combinations thereof.

The term "tampered dosage form" is defined for purposes of the present invention to mean that the dosage form has been manipulated by mechanical, thermal, and/or chemical means which changes the physical properties of the dosage form, e.g., to liberate the opioid agonist for immediate release if it is in sustained release form, or to make the opioid agonist available for inappropriate use such as administration by an alternate route, e.g., parenterally. The tampering can be, e.g., by means of crushing, shearing, grinding, chewing, dissolution in a solvent, heating, (e.g., greater than about 45° C.), or any combination thereof.

The term "substantially non-releasable form" for purposes of the present invention refers to an aversive agent that is not released or substantially not released at one hour after the intact dosage form containing an opioid agonist and at least one aversive agent is orally administered (i.e., without having been tampered with). The aversive agent in a substantially non-releasable form may be prepared in accordance with the teachings of U.S. application Ser. No. 09/781,081, entitled "Tamper Resistant Oral Opioid Agonist Formulations" filed Feb. 8, 2001, the disclosure of which is hereby incorporated by reference in its entirety, which describes a dosage form comprising an opioid antagonist in a substantially non-releasable form. For purposes of the present invention, the amount released after oral administration of the intact dosage form may be measured in-vitro via the dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37° C. Such a dosage form is also referred to as comprising a "sequestered aversive agent" depending on the agent or agents which are not released or substantially not released. In certain preferred embodiments of the invention, the substantially non-releasable form of the aversive agent is resistant to laxatives (e.g., mineral oil) used to manage delayed colonic transit and resistant to achlorhydric states. Preferably, the aversive agent is not released or not substantially released 4, 8, 12 and/or 24 hours after oral administration.

The phrase "analgesic effectiveness" is defined for purposes of the present invention as a satisfactory reduction in or elimination of pain, along with a tolerable level of side effects, as determined by the human patient.

The term "sustained release" is defined for purposes of the present invention as the release of the opioid analgesic from the oral dosage form at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range but below toxic levels over an extended period of time, e.g., from about 12 to about 24 hours as compared to an immediate release product. Preferably the sustained release is sufficient to provide a twice-a-day or a once-a-day formulation.

The term "particles" of aversive agent, as used herein, refers to granules, spheroids, beads or pellets comprising the aversive agent. In certain preferred embodiments, the aver-

sive agent particles are about 0.2 to about 2 mm in diameter, more preferably about 0.5 to about 2 mm in diameter.

The term "parenterally" as used herein includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, infusion techniques, or other methods of injection known in the art.

The term "inhaled" as used herein includes trans-mucosal, trans-bronchial, and trans-nasal abuse.

The term "bittering agent" as used herein includes a compound used to impart a bitter taste, bitter flavor, etc., to an abuser administering a tampered dosage form of the present invention.

The term "irritant" as used herein includes a compound used to impart an irritating or burning sensation to an abuser administering a tampered dosage form of the present invention.

The term "gelling agent" as used herein includes a compound or composition used to impart gel-like or thickening quality to a tampered dosage form upon the addition of moisture or liquid.

DETAILED DESCRIPTION OF THE INVENTION

The aversive agents of the present invention are preferably for use in connection with oral dosage forms including opioid analgesics, which provide valuable analgesia but which may be abused. This is particularly true for controlled release opioid analgesic products which have a large dose of opioid analgesic intended to be released over a period of time in each dosage unit. Drug abusers typically may take a controlled-release product and crush, shear, grind, chew, dissolve and/or heat, extract or otherwise damage the product so that the full contents of the dosage form become available for immediate absorption by injection, inhalation, and/or oral consumption.

In certain embodiments, the present invention comprises a method for preventing or deterring the abuse of opioid analgesics by the inclusion of at least one aversive agent in the dosage form with the opioid analgesic.

In certain alternative embodiments, the present invention comprises a method for preventing or deterring the abuse of drugs other than opioid analgesics which may also be the subject of abuse, by including at least one of the aversive agents described herein in a dosage form comprising the drug other than an opioid analgesic which is the subject of abuse.

In certain embodiments of the present invention wherein the dosage form includes an aversive agent comprising a bittering agent, various bittering agents can be employed including, for example and without limitation, natural, artificial and synthetic flavor oils and flavoring aromatics and/or oils, oleoresins and extracts derived from plants, leaves, flowers, fruits, and so forth, and combinations thereof. Nonlimiting representative flavor oils include spearmint oil, peppermint oil, eucalyptus oil, oil of nutmeg, allspice, mace, oil of bitter almonds, menthol and the like. Useful bittering agents can be artificial, natural and synthetic fruit flavors such as citrus oils including lemon, orange, lime, grapefruit, and fruit essences and so forth. Additional bittering agents include sucrose derivatives (e.g., sucrose octaacetate), chlorosucrose derivatives, quinine sulphate, and the like. The preferred bittering agent for use in the present invention is Denatonium Benzoate NF-Anhydrous, sold under the name Bitrex™ (Macfarlan Smith Limited, Edinburgh, UK).

With the inclusion of a bittering agent in the formulation, the intake of the tampered dosage form produces a bitter taste upon inhalation or oral administration which in certain embodiments spoils or hinders the pleasure of obtaining a high from the tampered dosage form, and preferably prevents the abuse of the dosage form.

A bittering agent may be added to the formulation in an amount of less than about 50% by weight preferably less than about 10% by weight, most preferably less than about 5% by weight of the dosage form, and most preferably in an amount ranging from about 0.1 to 1.0 percent by weight of the dosage form, depending on the particular bittering agent(s) used. A dosage form including a bittering agent preferably discourages improper usage of the tampered dosage form by imparting a disagreeable taste or flavor to the tampered dosage form.

In certain embodiments of the present invention wherein the dosage form includes an aversive agent comprising an irritant, various irritants can be employed including, for example and without limitation capsaicin, a capsaicin analog with similar type properties as capsaicin, and the like. Some capsaicin analogues or derivatives include for example and without limitation, resiniferatoxin, tinyatoxin, heptanoyl-isobutylamide, heptanoyl guaiacylamide, other isobutylamides or guaiacylamides, dihydrocapsaicin, homovanillyl octylester, nonanoyl vanillylamide, or other compounds of the class known as vanilloids. Resiniferatoxin is described, for example, in U.S. Pat. No. 5,290,816 (Blumberg), issued Mar. 1, 1994. U.S. Pat. No. 4,812,446 (Brand), issued Mar. 14, 1989, describes capsaicin analogs and methods for their preparation. Further, U.S. Pat. No. 4,424,205 (LaHann et al.), issued Jan. 3, 1984, cite Newman, "Natural and Synthetic Pepper-Flavored Substances" published in 1954 as listing pungency of capsaicin-like analogs. Ton et al., British Journal of Pharmacology, 10, pp. 175-182 (1955) discuss pharmacological actions of capsaicin and its analogs.

With the inclusion of an irritant (e.g., capsaicin) in the dosage form, when the dosage form is tampered with, the capsaicin imparts a burning or discomforting quality to the abuser to preferably discourage the inhalation, injection, or oral administration of the tampered dosage form, and preferably to prevent the abuse of the dosage form. Suitable capsaicin compositions include capsaicin (trans 8-methyl-N-vanillyl-6-noneamide or analogues thereof in a concentration between about 0.00125% and 50% by weight, preferably between about 1 and about 7.5% by weight, and most preferably, between about 1 and about 5% by weight of the dosage form.

In certain embodiments of the present invention wherein the dosage form includes an aversive agent comprising a gelling agent, various gelling agents can be employed including, for example and without limitation, sugars or sugar derived alcohols, such as mannitol, sorbitol, and the like, starch and starch derivatives, cellulose derivatives, such as microcrystalline cellulose, sodium cahoxymethyl cellulose, methylcellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose, attapulgites, bentonites, dextrins, alginates, carrageenan, gum tragacanth, gum acacia, guar gum, xanthan gum, pectin, gelatin, kaolin, lecithin, magnesium aluminum silicate, the carbomers and carbopols, polyvinylpyrrolidone, polyethylene glycol, polyethylene oxide, polyvinyl alcohol, silicon dioxide, surfactants, mixed surfactant/wetting agent systems, emulsifiers, other polymeric materials, and mixtures thereof, etc. certain preferred embodiments, the gelling agent is xanthan gum. In other preferred embodiments, the gelling agent of the present invention is pectin. The pectin or pectic substances useful for this invention include not only purified or isolated pectates but also crude natural pectin sources, such as apple, citrus or sugar beet residues which have been subjected, when necessary, to esterification or de-esterification,

e.g., by alkali or enzymes. Preferably, the pectins used in this invention are derived from citrus fruits such as lime, lemon, grapefruit, and orange.

With the inclusion of a gelling agent in the dosage form, when the dosage form is tampered with, the gelling agent preferably imparts a gel-like quality to the tampered dosage form which preferably spoils or hinders the pleasure of obtaining a rapid high from the tampered dosage form due to the gel like consistency in contact with the mucous membrane, and in certain embodiments, prevents the abuse of the dosage form by minimizing absorption, e.g. in the nasal passages. A gelling agent may be added to the formulation in a ratio of gelling agent to opioid agonist of from about 1:40 to about 40:1 by weight, preferably from about 1:1 to about 30:1 by weight, and more preferably from about 2:1 to about 10:1 by weight of the opioid agonist. In certain alternative embodiments, the gelling agent may be present in a ratio to the opioid agonist of from about 1:15 to about 15:1, preferably in a ratio of from about 1:8 to about 8:1, and more preferably from about 1:3 to about 3:1 by weight of the opioid agonist.

In certain other embodiments, the dosage form forms a viscous gel after the dosage form is tampered with, dissolved in an aqueous liquid (from about 0.5 to about 10 ml and preferably from 1 to about 5 ml), causing the resulting mixture to have a viscosity of at least about 10 cP. Most preferably, the resulting mixture will have a viscosity of at least about 60 cP.

In certain other embodiments, the dosage form forms a viscous gel after the dosage form is tampered with, dissolved in an aqueous liquid (from about 0.5 to about 10 ml and preferably from 1 to about 5 ml) and then heated (e.g., greater than about 45° C.), causing the resulting mixture to have a viscosity of at least about 10 cP. Most preferably, the resulting mixture will have a viscosity of at least about 60 cP.

In certain embodiments, the dosage form may include one or more of the aforementioned aversive agents. For safety reasons, the amount of the bittering agent, irritant, or gelling agent in a formulation of the present invention should not be toxic to humans.

In certain embodiments, the aversive agent included in the dosage form may be in a substantially non-releasable form. Where the aversive agent is in a substantially non-releasable form, the substantially non-releasable form of the aversive agent comprises an aversive agent that is formulated with one or more pharmaceutically acceptable hydrophobic materials, such that the aversive agent is not released or substantially not released during its transit through the gastrointestinal tract when administered orally as intended, without having been tampered with.

In certain embodiments of the present invention, the substantially non-releasable form of the aversive agent is vulnerable to mechanical, thermal and/or chemical tampering, e.g., tampering by means of crushing, shearing, grinding, chewing and/or dissolution in a solvent in combination with heating (e.g., greater, than about 45° C.) of the oral dosage form. When the dosage form is tampered with, the integrity of the substantially non-releasable form of the aversive agent will be compromised, and the aversive agent will be made available to be released. In certain embodiments, when the dosage form is chewed, crushed or dissolved and heated in a solvent, the release of the aversive agent hinders, deters or prevents the administration of the tampered dosage form orally, intranasally, parenterally and/or sublingually.

The opioid agonists useful in the present invention include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, mixtures of any of the foregoing, salts of any of the foregoing, and the like. In certain embodiments, the amount of the opioid agonist in the claimed opioid composition may be about 75 ng to about 750 mg.

In certain preferred embodiments, the opioid agonist is selected from the group consisting of hydrocodone, morphine, hydromorphone, oxycodone, codeine, levorphanol, meperidine, methadone, oxymorphone, buprenorphine, fentanyl and derivatives thereof, dipipanone, heroin, tramadol, etorphine, dihydroetorphine, butorphanol, levorphanol, or salts thereof or mixtures thereof. In certain preferred embodiments, the opioid agonist is oxycodone or hydrocodone.

In embodiments in which the opioid analgesic comprises hydrocodone, dosage forms may include analgesic doses from about 2 mg to about 50 mg of hydrocodone bitartrate. In embodiments in which the opioid analgesic comprises hydromorphone the dosage form may include from about 2 mg to about 64 mg hydromorphone hydrochloride. In embodiments in which the opioid analgesic comprises morphine, the dosage form may include from about 2.5 mg to about 800 mg morphine sulfate, by weight. In embodiments in which the opioid analgesic comprises oxycodone, the dosage form may include from about 2.5 mg to about 320 mg oxycodone hydrochloride. The dosage form may contain more than one opioid analgesic to provide a therapeutic effect. Alternatively, the dosage form may contain molar equivalent amounts of other salts of the opioids useful in the present invention.

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple central nervous system and gastrointestinal actions. Chemically, hydrocodone is 4,5-epoxy-3-methoxy-17-methylmorphinan-6-one, and is also known as dihydrocodeinone. Like other opioids, hydrocodone may be habit forming and may produce drug dependence of the morphine type. In excess doses hydrocodone, like other opium derivatives, will depress respiration.

Oral hydrocodone is also available in Europe (Belgium, Germany, Greece, Italy, Luxembourg, Norway and Switzerland) as an antitussive agent. A parenteral formulation is also available in Germany as an antitussive agent. For use as an analgesic, hydrocodone bitartrate is commercially available in the United States only as a fixed combination with non-opiate drugs (i.e., ibuprofen, acetaminophen, aspirin, etc.) for relief of moderate or moderately severe pain.

A common dosage form of hydrocodone is in combination with acetaminophen, and is commercially available, e.g., as Lortab® in the U.S. from UCB Pharma. Inc. as 2.5/500 mg, 5/500 mg, 7.5/500 mg and 10/500 mg hydrocodone/acetaminophen tablets. Tablets are also available in the ratio of 7.5 mg hydrocodone bitartrate and 650 mg acetaminophen; and 7.5 mg hydrocodone bitartrate and 750 mg acetaminophen. Hydrocodone in combination with aspirin is given in an oral dosage form to adults generally in 1-2 tablets every 4-6 hours

as needed to alleviate pain. The tablet form is 5 mg hydrocodone bitartrate and 224 mg aspirin with 32 mg caffeine; or 5 mg hydrocodone bitartrate and 500 mg aspirin. A relatively new formulation comprises hydrocodone bitartrate and ibuprofen. Vicoprofen®, commercially available in the U.S. from Knoll Laboratories, is a tablet containing 7.5 mg hydrocodone bitartrate and 200 mg ibuprofen. The present invention is contemplated to encompass all such formulations, with the inclusion of one or more aversive agents as described herein.

Oxycodone, chemically known as 4,5-expoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, is an opioid agonist whose principal therapeutic action is analgesia. Other therapeutic effects of oxycodone include anxiolysis, euphoria and feelings of relaxation. The precise mechanism of its analgesic action is not known, but specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone is commercially available in the United States, e.g., as Oxycontin® from Purdue Pharma L.P. as controlled-release tablets for oral administration containing 10 mg, 20 mg, 40 mg or 80 mg oxycodone hydrochloride, and as OxyIR™, also from Purdue Pharma L.P., as immediate-release capsules containing 5 mg oxycodone hydrochloride. The present invention is contemplated to encompass all such formulations, with the inclusion of one or more aversive agents as described herein.

Additionally, agents other than opioid analgesics which are subject to abuse may be used in accordance with the present invention in place of the opioid analgesics in the dosage form. Certain agents include, for example and without limitation, tranquilizers, CNS depressants, CNS stimulants, sedative hypnotics and the like. More specifically, barbiturates such as phenobarbital, secobarbital, pentobarbital, butabarbital, talbutal, aprobarbital, mephobarbital, butalbital, pharmaceutically acceptable salts thereof, and the like; benzodiazepines such as diazepam, chlordiazepoxide, alprazolam, triazolam, estazolam, clonazepam, flunitrazepam, pharmaceutically acceptable salts thereof, and the like; stimulants such as gamma-hydroxybutyrate, dextroamphetamine, methylphenidate, sibutramine, methylenedioxymethamphetamine, pharmaceutically acceptable salts thereof, and the like; and other agents such as marinol, meprobamate, carisoprodol, pharmaceutically acceptable salts thereof and the like.

Preparation of Aversive Agent in a Substantially Non-Releasable Form

In certain embodiments of the present invention, an aversive agent in a substantially non-releasable form may be prepared by combining the aversive agent with one or more of a pharmaceutically acceptable hydrophobic material. For example, aversive agent particles may be coated with coating that substantially prevents the release of the aversive agent, the coating comprising the hydrophobic materials(s). Another example would be an aversive agent that is dispersed in a matrix that renders the aversive agent substantially non-releasable, the matrix comprising the hydrophobic materials(s). In certain embodiments, the pharmaceutically acceptable hydrophobic material comprises a cellulose polymer selected from the group consisting of ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate and cellulose triacetate. An example of ethylcellulose is one that has an ethoxy content of 44 to 55%. Ethylcellulose may be used in the form of an alcoholic solution. In certain other embodiments, the hydrophobic material comprises polylactic acid, polyglycolic acid or a co-polymer of the polylactic and polyglycolic acid.

In certain embodiments, the hydrophobic material may comprise a cellulose polymer selected from the group consisting of cellulose ether, cellulose ester, cellulose ester ether, and cellulose. The cellulosic polymers have a degree of substitution, D.S., on the anhydroglucose unit, from greater than zero and up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include a polymer selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono, di, and tricellulose alkanylates, mono, di, and tricellulose aroylates, and mono, di, and tricellulose alkenylates. Exemplary polymers include cellulose acetate having a D.S. and an acetyl content up to 21%; cellulose acetate having an acetyl content up to 32 to 39.8%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%.

More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2 to 45 and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacylate having a D.S. of 2.9 to 3 such as cellulose triacetate, cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, and coesters of cellulose such as cellulose acetate butyrate, cellulose acetate octanoate butyrate and cellulose acetate propionate.

Additional cellulose polymers useful for preparing an aversive agent in a substantially non-releasable form include acetaldehyde dimethyl cellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, and cellulose acetate dimethylaminocellulose acetate.

Acrylic polymers useful for preparation of the aversive agent in a substantially non-releasable form include, but are not limited to, acrylic resins comprising copolymers synthesized from acrylic and methacrylic acid esters (e.g., the copolymer of acrylic acid lower alkyl ester and methacrylic acid lower alkyl ester) containing about 0.02 to 0.03 mole of a tri (lower alkyl) ammonium group per mole of the acrylic and methacrylic monomers used. An example of a suitable acrylic resin is a polymer manufactured by Rohm Pharma GmbH and sold under the Eudragit® RS trademark. Eudragit RS30D is preferred. Eudragit® RS is a water insoluble copolymer of ethyl acrylate (EA), methyl methacrylate (MM) and trimethylammoniumethyl methacrylate chloride (TAM) in which the molar ratio of TAM to the remaining components (EA and MM) is 1:40. Acrylic resins such as Eudragit® RS may be used in the form of an aqueous suspension.

In certain embodiments of the invention, the acrylic polymer may be selected from the group consisting of acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate)

copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate co-polymers.

When the aversive agent in a substantially non-releasable form comprises aversive agent particles coated with a coating that renders the aversive agent substantially non-releasable, and when a cellulose polymer or an acrylic polymer is used for preparation of the coating composition, suitable plasticizers, e.g., acetyl triethyl citrate and/or acetyl tributyl citrate may also be admixed with the polymer. The coating may also contain additives such as coloring agents, talc and/or magnesium stearate, which are well known in the coating art.

The coating composition may be applied onto the aversive agent particles by spraying it onto the particles using any suitable spray equipment known in the art. For example, a Wuster fluidized-bed system may be used in which an air jet, injected from underneath, fluidizes the coated material and effects drying while the insoluble polymer coating is sprayed on. The thickness of the coating will depend on the characteristics of the particular coating composition being used. However, it is well within the ability of one skilled in the art to determine by routine experimentation the optimum thickness of a particular coating required for a particular dosage form of the present invention.

The pharmaceutically acceptable hydrophobic material useful for preparing an aversive agent in a substantially non-releasable form includes a biodegradable polymer comprising a poly(lactic/glycolic acid) ("PLGA"), a polylactide, a polyglycolide, a polyanhydride, a polyorthoester, polycaprolactones, polyphosphazenes, polysaccharides, proteinaceous polymers, polyesthers, polydioxanone, polygluconate, polylactic-acid-polyethylene oxide copolymers, poly(hydroxybutyrate), polyphosphoesther or mixtures or blends of any of these.

In certain embodiments, biodegradable polymer comprises a poly(lactic/glycolic acid), a copolymer of lactic and glycolic acid, having molecular weight of about 2,000 to about 500,000 daltons. The ratio of lactic acid to glycolic acid is from about 100:0 to about 25:75, with the ratio of lactic acid to glycolic acid of 65:35 being preferred.

Poly(lactic/glycolic acid) may be prepared by the procedure set forth in U.S. Pat. No. 4,293,539 (Ludwig et al.), the disclosure of which is hereby incorporated by reference in its entirety. In brief, Ludwig prepares the copolymer by condensation of lactic acid and glycolic acid in the presence of a readily removable polymerization catalyst (e.g., a strong acid ion-exchange resin such as Dowex HCR-W2-H). The amount of catalyst is not critical to the polymerization, but typically is from about 0.01 to about 20 parts by weight relative to the total weight of combined lactic acid and glycolic acid. The polymerization reaction may be conducted without solvents at a temperature from about 100° C. to about 250° C. for about 48 to about 96 hours, preferably under a reduced pressure to facilitate removal of water and by-products. Poly(lactic/glycolic acid) is then recovered by filtering the molten reaction mixture in an organic solvent such as dichloromethane or acetone and then filtering to remove the catalyst.

Once the aversive agent in a substantially non-releasable form is prepared, it may be combined with an opioid agonist, along with conventional excipients known in the art, to prepare the oral dosage form of the present invention. It is contemplated that a bittering agent or capsaicin would be the most likely aversive agent to be included in a sequestered formulation. The polymers and other ingredients above may also be utilized to formulate the aversive agents to slow release or delay release as disclosed above.

In certain preferred embodiments of the invention, the oral dosage form is a capsule or a tablet. When being formulated as a tablet, the aversive agent and opioid agonist may be combined with one or more inert, non-toxic pharmaceutical excipients which are suitable for the manufacture of tablets. Such excipients include, for example, an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate.

The oral dosage form of the present invention may be formulated to provide immediate release of the opioid agonist contained therein. In other embodiments of the invention, however, the oral dosage form provides sustained-release of the opioid agonist.

In certain embodiments, the oral dosage forms providing sustained release of the opioid agonist may be prepared by admixing the aversive agent in a substantially non-releasable form with the opioid agonist and desirable pharmaceutical excipients to provide a tablet, and then coating the tablet with a sustained-release tablet coating.

In certain embodiments of the invention, sustained release opioid agonist tablets may be prepared by admixing the substantially non-releasable form of an aversive agent with an aversive agent in a matrix that provides the tablets with sustained-releasing properties.

Dosage Forms

The opioid analgesic formulation in combination with one or more aversive agents can be formulated as an immediate release formulation or controlled release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The controlled release dosage form may include a controlled release material which is incorporated into a matrix along with the opioid analgesic. In addition, the aversive agent may be separate from the matrix, or incorporated into the matrix.

The controlled release dosage form may optionally comprise particles containing or comprising the opioid analgesic, wherein the particles have diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. Additionally, the aversive agent may be incorporated into these particles, or may be incorporated into a tablet or capsule containing these particles. Preferably, the particles are film coated with a material that permits release of the opioid analgesic at a controlled rate in an environment of use. The film coat is chosen so as to achieve, in combination with the other stated properties, a desired in-vitro release rate. The controlled release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

In certain embodiments, the dosage forms of the present invention comprise normal release matrixes containing the opioid analgesic and the aversive agent.

Coated Beads

In certain embodiments of the present invention a hydrophobic material is used to coat inert pharmaceutical beads such as nu panel 18/20 beads comprising an opioid analgesic, and a plurality of the resultant solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media. The one or more aversive agents may also be coated onto the beads comprising the opioid

analgesic, may be prepared as separate beads and then combined in a dosage form including the controlled release beads comprising an opioid analgesic, or the one or more aversive agents may be mixed in the dosage form with the controlled release beads comprising the opioid analgesic. In preferred embodiments where the opioid analgesic and the aversive agent are mixed in a capsule as different beads, the beads have an exact or similar appearance in order to deter an abuser from manually separating the beads prior to abuse in order to avoid the aversive substance. In tablet dosage forms, the aversive agent is preferably not included as a distinct layer which can be easier to separate from the active agent, although the present invention docs encompass these embodiments.

The controlled release bead formulations of the present invention slowly release the opioid analgesic, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which a plasticizer is added to the hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with an opioid analgesic are prepared, e.g., by dissolving the opioid analgesic in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Thereafter, the one or more aversive agent is optionally added to the beads prior to coating. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the opioid to the beads. For example, a product which includes hydroxypropylmethylcellulose, etc. (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the opioid analgesic from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat® or Surelease®, may be used. If Surelease® is used, it is not necessary to separately add a plasticizer. Alternatively, preformulated aqueous dispersions of acrylic polymers such as Eudragit® can be used.

Plasticized hydrophobic material may be applied onto the substrate comprising the opioid analgesic by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined controlled release of said opioid analgesic when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the opioid analgesic, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry®, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the opioid analgesic from the controlled release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The controlled release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The controlled release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semipermeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The controlled release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864. The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

Matrix Formulations

In certain embodiments of the present invention, the sustained release formulation is achieved via a matrix optionally having a controlled release coating as set forth herein. The present invention may also utilize a sustained release matrix that affords in-vitro dissolution rates of the opioid analgesic within desired ranges and releases the opioid analgesic in a pH-dependent or pH-independent manner.

A non-limiting list of suitable sustained-release materials which r-ay be included in a sustained-release matrix according to the invention includes hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials, waxes, shellac, and oils such as hydrogenated castor oil and hydrogenated vegetable oil. However, any pharmaceutically acceptable hydrophobic or hydrophilic sustained-release material which is capable of imparting sustained-release of the opioid analgesic may be used in accordance with the present invention. Preferred sustained-release polymers include alkylcelluloses such as ethylcellulose, acrylic and methacrylic acid polymers and copolymers; and cellulose ethers, especially hydroxyalkylcelluloses (especially hydroxypropylmethylcellulose) and carboxyalkylcelluloses. Preferred acrylic and methacrylic acid polymers and copolymers include methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, ethyl acrylate, trimethyl ammonioethyl methacrylate, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copoly-

mer, poly(methylmethacrylate), poly(methacrylicacid) (anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. Certain preferred embodiments utilize mixtures of any of the foregoing sustained-release materials in the matrix of the invention.

The matrix also may include a binder. In such embodiments, the binder preferably contributes to the sustained-release of the opioid analgesic or pharmaceutically acceptable salt thereof from the sustained-release matrix.

If an additional hydrophobic binder material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive. In certain preferred embodiments, a combination of two or more hydrophobic binder materials are included in the matrix formulations.

Preferred hydrophobic binder materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils, natural and synthetic waxes and polyalkylene glycols. Hydrocarbons having a melting point of between 25° and 90° C. are preferred. Of the long-chain hydrocarbon binder materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 80% (by weight) of at least one digestible, long chain hydrocarbon.

In certain embodiments, the hydrophobic binder material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30 to about 100° C. In certain preferred embodiments, the dosage form comprises a sustained release matrix comprising an opioid analgesic; one or more aversive agents; and at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form may be determined, inter alia, by the precise rate of opioid analgesic release required. The aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the aliphatic alcohol in the present oral dosage form may be determined, as above, by the precise rate of opioid analgesic release required. It may also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between about 20% and about 50% (by wt) of the aliphatic alcohol. When a polyalkylene glycol is present in the oral dosage form, then the combined weight of the aliphatic alcohol and the polyalkylene glycol preferably constitutes between about 20% and about 50% (by wt) of the total dosage form.

In one preferred embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the opioid analgesic from the formulation. In certain embodiments, a ratio of the hydroxyalkyl cellulose to the aliphatic alcohol/polyalkylene glycol of between 1:1 and 1:4 is preferred, with a ratio of between 1:2 and 1:3 being particularly preferred.

In certain embodiments, the polyalkylene glycol may be, for example, polypropylene glycol, or polyethylene glycol which is preferred. The average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000, especially between 1,500 and 12,000.

Another suitable sustained-release matrix comprises an alkylcellulose (especially ethylcellulose), a C_{12} to C_{35} aliphatic alcohol and, optionally, a polyalkylene glycol.

In addition to the above ingredients, a sustained-release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, and glidants that are conventional in the pharmaceutical art.

In order to facilitate the preparation of a solid, sustained-release oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, sustained-release oral dosage form according to the present invention comprising incorporating an opioid analgesic in a sustained-release matrix. Incorporation in the matrix may be effected, for example, by:

(a) forming granules comprising at least one hydrophobic and/or hydrophilic material as set forth above (e.g., a water soluble hydroxyalkyl cellulose) together with the opioid analgesic, and at least one aversive agent;

(b) mixing the at least one hydrophobic and/or hydrophilic material containing granules with at least one C_{12}-C_{36} aliphatic alcohol, and

(c) optionally, compressing and shaping the granules.

The granules may be formed by any of the procedures well-known to those skilled in the art of pharmaceutical formulation. For example, in one preferred method, the granules may be formed by wet granulating the hydroxyalkyl cellulose, opioid analgesic, and one or more aversive agents with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the opioid analgesic. Optionally, the opioid analgesic and/or the one or more aversive agents are added extragranularly.

A sustained-release matrix can also be prepared by, e.g., melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic binder material, e.g., a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate a hydrophobic sustained-release material, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic binder material. Examples of sustained-release formulations prepared via melt-granulation techniques are found, e.g., in U.S. Pat. No. 4,861,598.

The additional hydrophobic binder material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve sustained release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial

release phases. Useful water-insoluble wax-like binder substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the opioid analgesic and at least one aversive agent, together with a sustained release material and preferably a binder material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded, e.g., using a twin-screw extruder, to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The matrix multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the opioid analgesic or pharmaceutically acceptable salt thereof for a time period of at least about 12 hours.

An optional process for preparing the melt extruded formulations of the present invention includes directly metering into an extruder a hydrophobic sustained release material, the opioid analgesic, one or more aversive agents, and an optional binder material; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into matrix multiparticulates having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

Optionally, the one or more aversive agents may be added to a dosage form including multiparticulates comprising opioid analgesic (without the one or more aversive agents).

Plasticizers, such as those described above, may be included in melt-extruded matrices. The plasticizer is preferably included as from about 0.1 to about 30% by weight of the matrix. Other pharmaceutical excipients, e.g., talc, mono or poly saccharides, lubricants and the like may be included in the sustained release matrices of the present invention as desired. The amounts included will depend upon the desired characteristic to be achieved.

The diameter of the extruder aperture or exit port can be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

A melt extruded matrix multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded matrix multiparticulate(s)" and "melt-extruded matrix multiparticulate system(s)" and "melt-extruded matrix particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic sustained release material as described herein. Preferably the melt-extruded matrix multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded matrix multiparticulates can be any geometrical shape within this size range. In certain embodiments, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared that include an effective amount of melt-extruded matrix multiparticulates within a capsule. For example, a plurality of the melt-extruded matrix multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastrointestinal fluid.

In another embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in *Remington's Pharmaceutical Sciences*, (Arthur Osol, editor), 1553-1593 (1980).

In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681 (Klimesch, et. al.).

Optionally, the sustained-release matrix multiparticulate systems, tablets, or capsules can be coated with a sustained release coating such as the sustained release coatings described herein. Such coatings preferably include a sufficient amount of hydrophobic and/or hydrophilic sustained-release material to obtain a weight gain level from about 2 to about 25 percent, although the overcoat may be greater depending upon, e.g., the desired release rate. The coating can optionally contain one or more of the aversive agents. In such embodiments, an optional second overcoat can be applied as to minimize the perception of the aversive agent when a dosage form of the present invention is administered intact.

The dosage forms of the present invention may further include combinations of melt-extruded matrix multiparticulates containing an opioid analgesic; one or more aversive agents; or mixtures thereof. Furthermore, the dosage forms can also include an amount of an immediate release opioid analgesic for prompt therapeutic effect. The immediate release opioid analgesic may be incorporated, e.g., as separate multiparticulates within a gelatin capsule, or may be coated on the surface of, e.g., melt extruded matrix multiparticulates.

The sustained-release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of sustained-release material, by varying the amount of plasticizer relative to other matrix constituents, by varying the amount of hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, melt-extruded formulations are prepared without the inclusion of the opioid analgesic; one or more aversive agents; or mixtures thereof; which is added thereafter to the extrudate. Such formulations typically will have the opioid analgesic; one or more aversive agents; or mixtures thereof blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. Such formulations may be advantageous, for example, when the opioid analgesic; one or more aversive agents; or mixtures thereof included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/or the retardant material.

Typical melt-extrusion production systems suitable for use in accordance with the present invention include a suitable extruder drive motor having variable speed and constant torque control, start-stop controls, and a meter. In addition, the production system will include a temperature control console which includes temperature sensors, cooling means and temperature indicators throughout the length of the extruder. In addition, the production system will include an extruder such as a twin-screw extruder which consists of two counter-rotating intermeshing screws enclosed within a cylinder or barrel having an aperture or die at the exit thereof.

The feed materials enter through a feed hopper and are moved through the barrel by the screws and are forced through the die into strands which are thereafter conveyed such as by a continuous movable belt to allow for cooling and being directed to a pelletizer or other suitable device to render the extruded ropes into the matrix multiparticulate system. The pelletizer can consist of rollers, fixed knife; rotating cutter and the like. Suitable instruments and systems are available from distributors such as C.W. Brabender Instruments, Inc. of South Hackensack, N.J. Other suitable apparatus will be apparent to those of ordinary skill in the art.

A further aspect of the invention is related to the preparation of melt-extruded matrix multiparticulates as set forth above in a manner which controls the amount of air included in the extruded product. By controlling the amount of air included in the extrudate, the release rate of the opioid analgesic, one or more aversive agents, or mixtures thereof may be altered.

Thus, in a further aspect of the invention, the melt-extruded product is prepared in a manner which substantially excludes air during the extrusion phase of the process. This may be accomplished, for example, by using a Leistritz extruder having a vacuum attachment. The extruded matrix multiparticulates prepared according to the invention using the Leistritz extruder under vacuum provides a melt-extruded product having different physical characteristics. In particular, the extrudate is substantially non-porous when magnified, e.g., using a scanning electron microscope which provides an SEM (scanning electron micrograph). Such substantially non-porous formulations may provide a faster release of the therapeutically active agent, relative to the same formulation prepared without vacuum. SEMs of the matrix multiparticulates prepared using an extruder under vacuum appear very smooth, and the multiparticulates tend to be more robust than those multiparticulates prepared without vacuum. It has been observed that in at least certain formulations, the use of extrusion under vacuum provides an extruded matrix multiparticulate product which is more pH-dependent than its counterpart formulation prepared without vacuum.

Alternatively, the melt-extruded product is prepared using a Werner-Pfleiderer twin screw extruder.

In certain embodiments, a spheronizing agent is added to a granulate or matrix multiparticulate and then spheronized to produce sustained release spheroids. The spheroids are then optionally overcoated with a sustained release coating by methods such as those described above.

Spheronizing agents which may be used to prepare the matrix multiparticulate formulations of the present invention include any art-known spheronizing agent. Cellulose derivatives are preferred, and microcrystalline cellulose is especially preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (TradeMark, FMC Corporation). The spheronizing agent is preferably included as about 1 to about 99% of the matrix multiparticulate by weight.

In certain embodiments, in addition to the opioid analgesic, one or more aversive agents, and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose.

In certain embodiments, a sustained release coating is applied to the sustained release spheroids, granules, or matrix multiparticulates. In such embodiments, the sustained-release coating may include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein. The coating is preferably derived from an aqueous dispersion of the hydrophobic sustained release material.

In certain embodiments, it is necessary to overcoat the sustained release spheroids, granules, or matrix multiparticulates comprising the opioid analgesic, one or more aversive agents, and sustained release carrier with a sufficient amount of the aqueous dispersion of, e.g., alkylcellulose or acrylic polymer, to obtain a weight gain level from about 2 to about 50%, e.g., about 2 to about 25%, in order to obtain a sustained-release formulation. The overcoat may be lesser or greater depending upon, e.g., the desired release rate, the inclusion of plasticizer in the aqueous dispersion and the manner of incorporation of the same. Cellulosic materials and polymers, including alkylcelluloses, are sustained release materials well suited for coating the sustained release spheroids, granules, or matrix multiparticulates according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

One commercially available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly to the sustained release spheroids, granules, or matrix multiparticulates.

In other preferred embodiments of the present invention, the sustained release material comprising the sustained-release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in the National Formulary (NF) XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical proper-

ties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Röhm GMBH and Co. Kg Darmstadt, Germany. There are several different types of Eudragit®. For example, Eudragit E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit® does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit RL and Eudragit RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent; however, dosage forms coated with Eudragit RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL300 and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained-release formulation having a desirable dissolution profile. Desirable sustained-release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL:Eudragit® 90% RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L. In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic sustained release material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained-release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained-release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

In certain embodiments, the uncoated/coated sustained release spheroids, granules, or matrix multiparticulates containing the opioid analgesic; and one or more aversive agents; are cured until an endpoint is reached at which the sustained release spheroids, granules, or matrix multiparticulates provide a stable dissolution of the opioid. The curing endpoint may be determined by comparing the dissolution profile (curve) of the dosage form immediately after curing to the dissolution profile (curve) of the dosage form after exposure to accelerated storage conditions of, e.g., at least one month at a temperature of 40° C. and a relative humidity of 75%. Cured formulations are described in detail in U.S. Pat. Nos. 5,273,760; 5,286,493; 5,500,227; 5,580,578; 5,639,476; 5,681,585; and 6,024,982. Other example's of sustained-release formulations and coatings which may be used in accordance with the present invention include those described in U.S. Pat. Nos. 5,324,351; 5,356,467; and 5,472,712.

In addition to the above ingredients, the spheroids, granules, or matrix multiparticulates may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the formulation if desired. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association (1986), incorporated by reference herein.

It has further been found that the addition of a small amount of talc to the sustained release coating reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

Osmotic Dosage Forms

Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer (containing the opioid analgesic and optionally one or more aversive agents) and a delivery or push layer (which may contain the one or more aversive agents), wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which the opioid analgesic can be pumped, diffuse or migrate through a fiber, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of

use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The passageway can have any shape, such as round, triangular, square and elliptical, for assisting in the sustained metered release of opioid analgesic from the dosage form. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are described in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,063,064 and 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a sustained-release rate are described in U.S. Pat. Nos. 4,200,098 and 4,285,987.

In certain embodiments, the bilayer core comprises a drug layer with opioid analgesic and a displacement or push layer optionally containing the one or more aversive agents. The one or more aversive agents may optionally be included in the drug layer instead of or in addition to being included in the push layer. In certain embodiments the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)_n.H_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) revresented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethylcellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as osmogel), whereby they push the contents of the drug layer from the osmotic dosage form.

The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulfate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulfate, sodium sulfate, potassium phosphate, glucose, fructose and maltose.

The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkylcellulose is represented by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropyl isopropyl cellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alphatocopherol, and propylgallate.

In certain alternative embodiments, the dosage form comprises a substantially homogenous core comprising opioid analgesic, one or more aversive agents, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc.). The substantially homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the opioid analgesic, and the one or more aversive agents.

In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkinylates. The poly(cellulose) used for the Present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethycellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,876; semipermeable polymers as dis-

closed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable crosslinked polystyrenes; semipermeable cross-linked poly(sodium styrene sulfonate); semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride); and semipermeable polymers possessing a fluid permeability of 2.5×10^{-8} to 2.5×10^{-2} (cm^2/hr·atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present invention are known in the art in U.S. Pat. Nos. 3,845,770; 3,916,899 and 4,160,020; and in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder. An example of a binder includes, but is not limited to a therapeutically acceptable vinyl polymer having a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinyl-pyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laureate, and vinyl stearate. Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.

Transdermal Delivery Systems

The formulations of the present invention may be formulated as a transdermal delivery system, such as transdermal patches. In certain embodiments of the present invention, a transdermal patch comprises an opioid agonist contained in a reservoir or a matrix, and an adhesive which allows the transdermal device to adhere to the skin, allowing the passage of the active agent from the transdermal device through the skin of the patient, with the inclusion of the aversive agents as disclosed herein which are not releasable when the dosage form is administered intact but which are releasable when the dosage form is broken or tampered with in order to release the opioid from the transdermal system.

Transdermal delivery system providing a controlled-release of an opioid agonist is known. For example, Duragesic® patch (commercially available from Janssen Pharmaceutical) contains an opioid agonist (fentanyl) and is said to provide adequate analgesia for up to 48 to 72 hours (2 to 3 days). This formulation can be reformulated with an aversive agent as disclosed herein.

There are several types of transdermal formulations of buprenorphine reported in the literature. See, for example, U.S. Pat. No. 5,240,711 (Hille et al.), U.S. Pat. No. 5,225,199 (Hidaka et al.), U.S. Pat. No. 5,069,909 (Sharma et al.), U.S. Pat. No. 4,806,341 (Chien et al.), and U.S. Pat. No. 5,026,556 (Drust et al.), all of which are hereby incorporated by reference. These transdermal devices can also be reformulated with the aversive agents as disclosed herein.

The transdermal delivery system used in the present invention may also be prepared in accordance with U.S. Pat. No. 5,069,909 (Sharma et al.), hereby incorporated by reference. This patent describes a laminated composite for administering buprenorphine transdermally to treat pain. The transdermal delivery system used in the present invention may also be prepared in accordance with U.S. Pat. No. 4,806,341 (Chien et al.), hereby incorporated by reference. This patent describes a transdermal morphinan narcotic analgesic or antagonist (including buprenorphine) pharmaceutical polymer matrix dosage unit having a backing layer which is substantially impervious to the buprenorphine, and a polymer matrix disc layer which is adhered to the backing layer and which has microdisposed therein effective dosage amounts of the buprenorphine.

The transdermal delivery system used in the present invention may also be that described in U.S. Pat. No. 5,026,556 (Drust et al.), hereby incorporated by reference. Therein, compositions for the transdermal delivery of buprenorphine comprise buprenorphine in a carrier of a polar solvent material selected from the group consisting of C_3-C_4 diols, C_3-C_6 triols, and mixtures thereof, and a polar lipid material selected from the group consisting of fatty alcohol esters, fatty acid esters, and mixtures thereof; wherein the polar solvent material and the lipid material are present in a weight ratio of solvent material:lipid material of from 60:40 to about 99:1. The transdermal delivery system used in the present invention may also be that described in U.S. Pat. No. 4,588,580 (Gale, et al.), hereby incorporated by reference. That system comprises a reservoir for the drug having a skin proximal, material releasing surface area in the range of about 5-100 cm^2 and containing between 0.1 and 50% by weight of a skin permeable form of the buprenorphine. The reservoir contains an aqueous gel comprising up to about 47-95% ethanol, 1-10% gelling agent, 0.1-10% buprenorphine, and release rate controlling means disposed in the flow path of the drug to the skin which limits the flux of the buprenorphine from the system through the skin.

The transdermal delivery system used in the present invention may also be that described in PCT/US01/04347 to Oshlack et al.

The present invention is contemplated to encompass all transdermal formulations, e.g., the technologies described above, with the inclusion of an aversive agent, such that the dosage form deters abuse of the opioid therein.

The aversive agent in non-releasable form when administered intact can be formulated in accordance with U.S. Pat. No. 5,149,538 to Granger, hereby incorporated by reference. Alternatively, the aversive agent and the opioid agonist can be separated from the opioid by a layer which becomes disrupted when the dosage form is tampered with, thereby mixing the aversive agent with the opioid agonist. Alternatively, a combination of both systems can be used.

Suppositories

The controlled release formulations of the present invention may be formulated as a pharmaceutical suppository for rectal administration comprising an opioid analgesic, and at least one aversive agent in a controlled release matrix, and a suppository vehicle (base). Preparation of Controlled Release Suppository Formulations is Described in, e.g., U.S. Pat. No. 5,215,758.

The suppository base chosen should be compatible with the agent(s) of the present invention. Further, the suppository

base is preferably non-toxic and nonirritating to mucous membranes, melts or dissolves in rectal fluids, and is stable during storage.

In certain preferred embodiments of the present invention for both water-soluble and water-insoluble drugs, the suppository base comprises a fatty acid wax selected from the group consisting of mono-, di- and triglycerides of saturated, natural fatty acids of the chain length C_{12} to C_{18}.

In preparing the suppositories of the present invention other excipients may be used. For example, a wax may be used to form the proper shape for administration via the rectal route. This system can also be used without wax, but with the addition of diluent filled in a gelatin capsule for both rectal and oral administration.

Examples of suitable commercially available mono-, di- and triglycerides include saturated natural fatty acids of the 12-18 carbon atom chain sold under the trade name Novata™ (types AB, AB, B, BC, BD, BBC, E, BCF, C, D and 299), manufactured by Henkel, and Witepsol™ (types H5, H12, H15, H175, H185, H119, H32, H35, H39, H42, W25, W31, W35, W45, S55, S58, E75, E76 and E85), manufactured by Dynamit Nobel.

Other pharmaceutically acceptable suppository bases may be substituted in whole or in part for the above-mentioned mono-, di- and triglycerides. The amount of base in the suppository is determined by the size (i.e. actual weight) of the dosage form, the amount of base (e.g., alginate) and drug used. Generally, the amount of suppository base is from about 20 percent to about 90 percent by weight of the total weight of the suppository. Preferably, the amount of base in the suppository is from about 65 percent to about 80 percent, by weight of the total weight of the suppository.

In certain embodiments of the dosage forms of the present invention may also include a surfactant. Surfactants useful in accordance with the present invention, include for example, ionic and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, including but not limited to castor oil derivatives, cholesterol, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polysorbates, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene compounds, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, ethoxylated alcohols, ethoxylated esters, ethoxylated amides, polyoxypropylene compounds, propoxylated alcohols, ethoxylated/propoxylated block polymers, propoxylated esters, alkanolamides, amine oxides, fatty acid esters of polyhydric alcohols, ethylene glycol esters, diethylene glycol esters, propylene glycol esters, glycerol esters, polyglycerol fatty acid esters, SPAN's (e.g., sorbitan esters), TWEEN's (i.e., sucrose esters), glucose (dextrose) esters, alkali metal sulfates, quaternary ammonium compounds, amidoamines, and aminimides, simethicone, lecithins, alcohols, phospholipids, and mixtures thereof.

Mixed surfactant/wetting agents useful in accordance with the present invention include, for example, sodium lauryl sulfate/polyethylene glycol (PEG) 6000 and sodium lauryl sulfate/PEG 6000/stearic acid, etc.

In certain embodiments of the present invention, the dosage form may also include an emulsifying agent. Emulsifying agents useful in accordance with the present invention include, for example, monoglycerides, sucrose/fatty acid esters, polyglycerol/fatty acid esters, sorbitan/fatty acid esters, lecithins, potassium and sodium salts of rosin acids and higher fatty acids, as well as sulfates and sulfonates of these acids, amine salts of hydroxylamines of long-chain fatty acid esters, quaternary ammonium salts such as stearyl-dimethylbenzylammonium chloride and tridecylbenzenehydroxyethylimidazole chloride, phosphoric esters of higher alcohols such as capryl and octyl alcohol, and monoesters of oleic acid and pentaerythritol such as sorbitan monooleates, and mixtures thereof.

The oral dosage form and methods for use of the present invention may further include, in addition to an opioid analgesic and at least one aversive agent, one or more drugs that may or may not act synergistically with the opioid analgesic. Thus, in certain embodiments, a combination of two opioid analgesics may be included in the dosage form. For example, the dosage form may include two opioid analgesics having different properties, such as half-life, solubility, potency, and a combination of any of the foregoing.

In yet further embodiments, one or more opioid analgesic is included and a further non-opioid drug is also included. Such non-opioid drugs would preferably provide additional analgesia, and include, for example, aspirin, acetaminophen; non-steroidal anti-inflammatory drugs ("NSAIDS"), e.g., ibuprofen, ketoprofen, etc.; N-methyl-D-aspartate (NMDA) receptor antagonists, e.g., a morphinan such as dextromethorphan or dextrorphan, or ketamine; cyclooxygenase-II inhibitors ("COX-II inhibitors"); and/or glycine receptor antagonists.

In certain preferred embodiments of the present invention, the invention allows for the use of lower doses of the opioid analgesic by virtue of the inclusion of an additional non-opioid analgesic, such as an NSAID or a COX-2 inhibitor. By using lower amounts of either or both drugs, the side effects associated with effective pain management in humans are reduced.

Suitable non-steroidal anti-inflammatory agents, including ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piro-profen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidornetacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and the like. Useful dosages of these drugs are well known to those skilled in the art.

N-methyl-D-aspartate (NMDA) receptor antagonists are well known in the art, and encompass, for example, morphinans such as dextromethorphan or dextrorphan, ketamine, or pharmaceutically acceptable salts thereof. For purposes of the present invention, the term "NMDA antagonist" is also deemed to encompass drugs that block a major intracellular consequence of NMDA-receptor activation, e.g. a ganglioside such as GM_1 or GT_{1b} a phenothiazine such as trifluoperazine or a naphthalenesulfonamide such as N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide. These drugs are stated to inhibit the development of tolerance to and/or dependence on addictive drugs, e.g., narcotic analgesics such as morphine, codeine, etc. in U.S. Pat. Nos. 5,321,012 and 5,556,838 (both to Mayer, et al.), and to treat chronic pain in U.S. Pat. No. 5,502,058 (Mayer, et al.), all of which are hereby incorporated by reference. The NMDA antagonist may be included alone, or in combination with a local anesthetic such as lidocaine, as described in these Mayer, et. al. patents.

The treatment of chronic pain via the use of glycine receptor antagonists and the identification of such drugs is described in U.S. Pat. No. 5,514,680 (Weber, et al.).

COX-2 inhibitors have been reported in the art and many chemical structures are known to produce inhibition of

cyclooxygenase-2. COX-2 inhibitors are described, for example, in U.S. Pat. Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213; 5,474,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311, all of which are hereby incorporated by reference. Certain preferred COX-2 inhibitors include celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), MK-966 (also known as Vioxx), nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, T-614; or combinations thereof. Dosage levels of COX-2 inhibitor on the order of from about 0.005 mg to about 140 mg per kilogram of body weight per clay are therapeutically effective in combination with an opioid analgesic. Alternatively, about 0.25 mg to about 7 g per patient per day of a COX-2 inhibitor is administered in combination with an opioid analgesic.

In yet further embodiments, a non-opioid drug can be included which provides a desired effect other than analgesia, e.g., antitussive, expectorant, decongestant, antihistamine drugs, local anesthetics, and the like.

The invention disclosed herein is meant to encompass the use of any pharmaceutically acceptable salts thereof of the disclosed opioid analgesics. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, secium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparginate, glutamate and the like.

Some of the opioid analgesics disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass the use of any such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. The use of all tautomers are intended to be encompassed by the present invention as well.

The oral dosage forms of the present invention may be in the form of tablets, troches, lozenges, powders or granules, hard or soft capsules, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, etc.

In certain embodiments, the present invention provides for a method of preventing abuse of an oral controlled release dosage form of an opioid analgesic comprising preparing the dosage forms as described above.

In certain embodiments, the present invention provides for a method of preventing diversion of an oral controlled release dosage form of an opioid analgesic comprising preparing the dosage forms as described above.

In certain embodiments, the present invention provides for a method of treating pain while at the same time reducing the risk of abuse by administering to a human patient the dosage forms described above.

As previously disclosed, the aversive agents of the present invention can be used for other drugs which can be the subject of abuse. Opioids, e.g., oxycodone are the preferred embodiments of the invention. However, it is contemplated that all of the disclosure herein With respect to opioid formulations containing the aversive agent(s) can be applied to formulations containing drugs of abuse other than opioids.

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

A 20 mg Oxycodone Formulation is Prepared Containing Xanthan Gum as the Aversive Agent

In this example, a small amount of xanthan gum is added to the oxycodone formulation during the granulation process. Other gelling agents such as curdlan, carrageenan, alginates, pectin, gelatin, furcelleran, agar, guar gum, locust bean gum, tara gum, tragacanth, acacia, glucomannans, karaya, starch and starch derivatives, egg white powder, lacto albumin, soy protein, Jargel, gellan gum, welan gum, rhamsan gum, and the like, could also be used as gelling agents. Other semi-synthetic materials such as chitosan, pullulan, polylaevulan, hydroxypropyl cellulose, methylcellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, ethylhydroxyethyl cellulose, all ether derivatives of cellulose, and the like, could also be used as alternate gelling materials.

TABLE 1

Ingredients	Amt/Unit (mg)	Amount/Batch (gm)
Oxycodone HCl	20.0	209.6*
Spray Dried Lactose	59.25	592.5
Povidone	5.0	50.0
Eudragit RS30D (solids)	10.0	100
Triacetin	2.0	20.0
Xanthan gum	9.0	90.0
Stearyl Alcohol	25.0	250.0
Talc	2.5	25.0
Magnesium Stearate	1.25	12.5
Opadry Pink Y-S-14518A	5.0	50.0

*adjusted for 99.6% assay and 4.2% residual moisture.

Process

1. Dispersion: Disperse Eudragit and Triacetin in an aqueous medium to form a Eudragit/Triacetin dispersion.
2. Granulation: Spray the Eudragit/Triacetin dispersion onto the oxycodone HCl, Spray Dried Lactose, xanthan gum and Povidone using a fluid bed granulator.
3. Milling: Discharge the granulation and pass through a mill.
4. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.
5. Milling: Pass the cooled granulation through a mill.
6. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.
7. Compression: Compress the granulation into tablets using a tablet press.

EXAMPLE 2

A 40 mg Oxycodone Formulation was Prepared Containing Xanthan Gum as the Aversive Agent

To determine the effect of varying amount of xanthan gum on the gelling property and dissolution rate of an oxycodone tablet, three levels of xanthan gum were added to 40 mg oxycodone granulation and compressed into tablets. Oxycodone recovery from water extraction of the tablet and the drug release rate was determined. The oxycodone granulation formulation of Example 2 is listed in Table 2 below.

TABLE 2

Ingredients	Amt/Unit (mg)
Oxycodone HCl	40.0
Spray Dried Lactose	39.25
Povidone	5.0
Eudragit RS30D (solids)	10.0
Triacetin	2.0
Stearyl Alcohol	25.0
Talc	2.5
Magnesium Stearate	1.25
Total	125

Examples 2A to 2C were prepared adding different amounts (3 mg, 5 mg, and 9 mg) of xanthan gum to a 125 mg oxycodone granulation of Example 2.

EXAMPLE 2A

Ingredients	Amt/Unit (mg)
Oxycodone granulation	125
Xanthan gum	3
Total	128

EXAMPLE 2B

Ingredients	Amt/Unit (mg)
Oxycodone granulation	125
Xanthan gum	5
Total	130

EXAMPLE 2C

Ingredients	Amt/Unit (mg)
Oxycodone granulation	125
Xanthan gum	9
Total	134

Process

1. Dispersion: Disperse Eudragit and Triacetin in an aqueous medium to form an Eudragit/Tracetin dispersion.
2. Granulation: Spray the Eudragit/Triacetin dispersion onto the Oxycodone Spray Dried Lactose and Povidone using a fluid bed granulator.
3. Milling: Discharge the granulation and pass through a mill.
4. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.
5. Milling: Pass the cooled granulation through a mill.
6. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.
7. Add xanthan gum (3 levels) to the granulation and mix well.
8. Compression: Compress the granulation into tablets using a tablet press.

EXAMPLE 3

A thickening agent, citrus pectin, was added to a placebo Oxycontin® 10 mg tablet (tablet without the drug present) and small amounts of water (e.g., 1 ml, 2 ml, and 3 ml) were added. The following results were obtained and compared and listed in Table 3:

TABLE 3

Formation of gel at different concentrations (Water, pectin and Oxycontin ® 10 mg placebo Tablet)

Weight of Pectin (mg)	Extraction Volume (1 ml)	Extraction Volume (2 ml)	Extraction Volume (3 ml)
25	THICK (55 cP)	THICK (34 cP)	THICK (24 cP)
50	THICKEST (375 cP)	THICKER (84 cP)	THICK (42 cP)
75	THICKEST (1830 cP)	THICKEST (154 cP)	THICKER (94 cP)

THIN (less than 10 cP): The solution can be filled into a syringe
THICK (10 cP to 60 cP): Although a syringe can be filled with this solution, it was hard to do.
THICKER (60 cP to 120 cP): Syringe cannot be filled without picking up large pockets of air.
THICKEST (120 cP or greater, e.g., up to 2000 cP or up to 5000 cP): The solution cannot be injected or is very difficult to draw into a syringe or to inject.

The results summarized in Table 3 indicate that all the extracts were hard or difficult to pull into an insulin syringe. The pectin can also emulsify the excipients in the aqueous mixture making their filtration difficult. The tablet's coating is suspended in the mixture resembling a paste. All the samples have a creamy texture and milk like color. Additionally, the filtration with cotton cannot remove the suspended material, thus the mixture would not appeal to an addict.

This experiment shows that an ingredient, such as pectin, could be added to the Oxycontin® Tablets to make the extraction of the oxycodone more difficult and thus reducing the potential for abuse. Addition of pectin to the tablets appears to make the extraction extremely difficult.

EXAMPLE 4

In Example 4, controlled release tablets containing an opioid agonist (oxycodone HCl) and gelling agent (microcrystalline cellulose) are prepared. The controlled release tablets comprise granulates comprising the opioid agonist and the gelling agent dispersed in a controlled release matrix. The granulates are combined with melted wax (stearyl alcohol) to produce waxed granulates, which are then milled and mixed with other excipients and compressed into tablets.

TABLE 4

Ingredient	Amt/unit (mg)	Amt/batch (kg)
Oxycodone HCl	10.00	11.00
Microcrystalline Cellulose	200.00	220.00
Spray Dried Lactose	68.75	75.62
Povidone	5.00	5.50
Triacetin	2.00	2.20
Stearyl Alcohol	25.00	27.50
Talc	2.50	2.75
Magnesium Stearate	1.25	1.38
Opadry White	5.00	5.50
Purified Water		31.16*
Total	319.50	382.61

*Remains in product as residual moisture only.

Process:

1. Granulation Place Oxycodone HCl, Spray Dried Lactose, water, Povidone, Microcrystalline Cellulose, and Triacetin into a fluid bed granulator.
2. Milling Pass the granulation through a rotating impeller mill.
3. Drying Dry granulation if moisture content is too high.
4. Waxing Melt Stearyl Alcohol and wax the above granulation by adding melted Stearyl Alcohol onto granulation while mixing.
5. Cooling Cool the waxed granulation in a fluid bed dryer.
6. Milling Pass the cooled waxed granulation through a rotating impeller mill.
7. Blending Blend the milled waxed granulation, Talc and Magnesium Stearate.
8. Compression Compress the resultant granulation using a tablet press.
9. Coating Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

EXAMPLE 5

In Example 5, controlled release tablets containing a opioid agonist (morphine sulfate) and gelling agent (hydroxyethyl cellulose) are prepared. The controlled release tablets comprise granulates comprising the opioid agonist and the gelling agent in a controlled-release matrix. The granulates are combined with melted wax (cetostearyl alcohol) to produce waxed granulates, which are then milled and mixed with other excipients and compressed into tablets.

TABLE 5

Ingredient	Amt/unit (mg)	Amt/batch (kg)
Morphine Sulfate (pentahydrate)	30.00	108.0
Spray Dried Lactose	69.5	250.2
Hydroxyethyl Cellulose	600.0	2160.0
Purified Water		75.9*
Cetostearyl Alcohol	35.0	126.0
Talc	3.0	10.8
Magnesium Stearate	2.0	7.2
Opadry Purple	3.0	10.8
Purified Water		61.2*
Total	742.50	2673

*Remains in product as residual moisture only.

Process:

1. Granulation Place Morphine Sulfate, Spray Dried Lactose, water, and Hydroxyethyl Cellulose in a mixer and granulate.
2. Drying Dry the above granulation in a fluid bed dryer.
3. Milling Pass the granulation through a mill.
4. Drying Dry granulation if moisture content is too high.
5. Waxing Melt Cetostearyl Alcohol and wax the above granulation by adding melted Cetostearyl Alcohol onto granulation while mixing.
6. Cooling Cool the waxed granulation in a fluid bed dryer.
7. Milling Pass the cooled waxed granulation through a mill.
8. Blending Blend the milled waxed granulation, Talc and Magnesium Stearate.
9. Compression Compress the resultant granulation using a tablet press.
10. Coating Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

In Examples 6-8, 10 mg oxycodone HCL tablets are prepared as follows:

EXAMPLE 6

A controlled release tablet having the formula listed below is prepared by wet granulating oxycodone hydrochloride (25.00 gm) with lactose monohydrate (417.5 gm), and hydroxyethyl cellulose (100.00 gm). The granules are sieved through a 12 mesh screen. The granules are then dried in a fluid bed dryer at 50° C. and sieved through a 16 mesh screen.

Molten cetostearyl alcohol (300.0 gm) is added to the warmed oxycodone containing granules, and the whole was mixed thoroughly. The mixture is allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

Purified Talc (15.0 gm), magnesium stearate (7.5 gm), and pectin (62.5 gm) are then added and mixed with the granules. The granules are then compressed into tablets.

TABLE 6

Ingredient	Amt/unit (mg)	Amt/batch (g)
Oxycodone HCl	10.00	25.0
Lactose Monohydrate	167.00	417.5
Hydroxyethylcellulose	40.00	100.0
Cetostearyl alcohol	120.00	300.0
Talc	6.0	15.0
Magnesium Stearate	3.0	7.5
Pectin	25.00	62.5

EXAMPLE 7

A controlled release tablet containing 10 mg of oxycodone and 50.00 mg of pectin and having the following formula is prepared in the same manner as in Example 6:

TABLE 7

Ingredient	Amt/unit (mg)	Amt/batch (g)
Oxycodone HCl	10.00	25.0
Lactose Monohydrate	167.00	417.5
Hydroxyethylcellulose	40.00	100.0
Cetostearyl alcohol	120.00	300.0
Talc	6.0	15.0
Magnesium Stearate	3.0	7.5
Pectin	50.00	125.00

EXAMPLE 8

A controlled release tablet containing 10 mg of oxycodone and 75.00 mg of pectin and having the following formula is prepared as in Example 6:

TABLE 8

Ingredient	Amt/unit (mg)	Amt/batch (g)
Oxycodone HCl	10.00	25.0
Lactose Monohydrate	167.00	417.5
Hydroxyethylcellulose	40.00	100.0
Cetostearyl alcohol	120.00	300.0

TABLE 8-continued

Ingredient	Amt/unit (mg)	Amt/batch (g)
Talc	6.0	15.0
Magnesium Stearate	3.0	7.5
Pectin	75.00	187.5

EXAMPLE 9

A 20 mg Oxycodone Formulation Containing a Bittering Agent is Prepared

In this example, a small amount of denatonium benzoate is added to an oxycodone formulation during the granulation process. The bitter taste would reduce the abuse of oxycodone by oral or intranasal route. The oxycodone formulation of Example 9 is listed in Table 9 below.

TABLE 9

Ingredients	Amt/Unit (mg)	Amount/Batch (gm)
Oxycodone HCl	20.0	209.6*
Spray Dried Lactose	59.25	592.5
Povidone	5.0	50.0
Eudragit RS30D (solids)	10.0	100
Triacetin	2.0	20.0
Denatonium benzoate	0.07	0.68
Stearyl Alcohol	25.0	250.0
Talc	2.5	25.0
Magnesium Stearate	1.25	12.5
Opadry Pink Y-S-14518A	5.0	50.0

*adjusted for 99.6% assay and 4.2% residual moisture.

Process

1. Dispersion: Dissolve denatonium benzoate in water and the solution is added to the Eudragit/Tracetin dispersion.
2. Granulation: Spray the Eudragit/Triacetin dispersion onto the Oxycodone HCl, Spray Dried Lactose and Povidone using a fluid bed granulator.
3. Milling: Discharge the granulation and pass through a mill.
4. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.
5. Milling: Pass the cooled granulation through a mill.
6. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.
7. Compression: Compress the granulation into tablets using a tablet press.

EXAMPLE 10

In Example 10, a substantially non-releasable form of a bittering agent (denatonium benzoate) is prepared by coating denatonium benzoate particles with a coating that renders the denatonium benzoate substantially non-releasable. The formula of Example 10 is listed in Table 10 below.

TABLE 10

Ingredients	Amt/unit (mg)
LOADING	
denatonium benzoate	0.07
Sugar Spheres (30/35 mesh)	50.0
Opadry White Y-5-7068	2.5
Purified Water	42.5*
OVERCOATING	
Opadry White Y-5-7068	3.02
Purified Water	17.11*
NON-RELEASE COATING (FOR RENDERING BITTERING AGENT SUBSTANTIALLY NON-RELEASABLE)	
Eudragit RS30D (dry wt.)	12.10
Triethyl Citrate	2.42
Talc	4.84
Purified Water	49.21*
OVERCOATING	
Opadry White Y-5-7068	4.12
Purified Water	23.35*
Total	79.07

*Remains in product as residual moisture only.

Process:

1. Solution Preparation Dissolve the denatonium benzoate in Purified Water. Once dissolved, add the Opadry White and continue mixing until a homogeneous dispersion is yielded.
2. Loading Apply the above dispersion onto the Sugar Spheres using a fluid bed coating machine.
3. Overcoating Prepare an overcoating solution by dispersing Opadry White in Purified Water. Apply this dispersion over the sugar spheres loaded with denatonium benzoate using a fluid bed coating machine.
4. Retardant Coating Prepare the non-release coating solution by mixing the Eudragit RS30D, Triethyl Citrate, Talc, and Purified Water. Apply this dispersion over the loaded and overcoated sugar spheres using a fluid bed coating machine.
5. Overcoating Prepare a second overcoating solution by dispersing Opadry White in Purified Water. Apply this dispersion over the non-release coated denatonium benzoate spheres using a fluid bed coating machine
6. Curing Cure the spheres at 45° C. for approximately 48 hours.

EXAMPLE 11

In Example 11, a substantially non-releasable form of a bittering agent (denatonium benzoate) is prepared as denatonium benzoate containing granulates. The granulates are comprised of denatonium benzoate dispersed in a matrix that renders the denatonium benzoate substantially non-releasable. The formula for Example 11 is listed in Table 11 below.

TABLE 11

Ingredient	Amt/unit (mg)
Denatonium benzoate	0.07
Dicalcium Phosphate	53.0
Poly (DI-Lactide-Co-Glycolide) polymer (PLGA) MW~ 100,000 Ethyl Acetate	12.0
Total	65.07

* Used as a vehicle for application of PLGA polymer.

Process:

1. Solution Preparation Dissolve PLGA in Ethyl Acetate by mixing.
2. Granulation Place the denatonium benzoate, and Dicalcium Phosphate in a fluid bed coating machine and granulate by spraying the above solution.

EXAMPLE 12

In Example 12, a substantially non-releasable form of a bittering agent (denatonium benzoate) is prepared as denatonium benzoate extruded pellets. The formula for Example 12 is listed in Table 12 below.

TABLE 12

Ingredient	Amt/unit (mg)
Denatonium benzoate	0.07
Eudragit RSPO	180.0
Stearyl Alcohol	55.0
Total	235.07

Process:

1. Milling Pass stearyl alcohol flakes through an impact mill.
2. Blending Mix Denatonium benzoate, Eudragit, and milled Stearyl Alcohol in a twin shell blender.
3. Extrusion Continuously feed the blended material into a twin screw extruder and collect the resultant strands on a conveyor.
4. Cooling Allow the strands to cool on the conveyor.
5. Pelletizing Cut the cooled strands into pellets using a Pelletizer.
6. Screening Screen the pellets and collect desired sieve portion.

EXAMPLE 13

Controlled Release Oxycodone 20 mg

In Example 17, a sustained release 20 mg oxycodone formulation is prepared having the formulation listed in Table 13 below.

TABLE 13

Ingredients	Amt/Unit (mg)
Oxycodone HCl	20.0
Spray Dried Lactose	59.25
Povidone	5.0
Eudragit RS30D (solids)	10.0
Triacetin	2.0
Stearyl Alcohol	25.0
Talc	2.5
Magnesium Stearate	1.25
Opadry Pink Y-S-14518A	4.0
Total	129.0

Process:

1. Granulation: Spray the Eudragit/Triacetin dispersion onto the Oxycodone HCl, Spray Dried Lactose and Povidone using a fluid bed granulator.
2. Milling: Discharge the granulation and pass through a mill.
3. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.
4. Milling: Pass the cooled granulation through a mill.
5. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.
6. Compression: Compress the granulation into tablets using a tablet pres.
7. Film coating: Apply an aqueous film coat to the tablets.

One or more aversive agents as described herein can be incorporated into the oxycodone tablets by one skilled in the art. The one or more aversive agents may be in releasable, non-releasable, or substantially non-releasable form or a combination thereof.

EXAMPLE 14

Controlled Release Hydrocodone

A sustained release hydrocodone formulation is prepared having the formula in Table 14 below.

TABLE 14

Ingredients	Amt/Unit (mg)	Amt/Batch (g)
Hydrocodone Bitartrate	15.0	320.0
Eudragit RSPO	76.0	1520.0
Eudragit RLPO	4.0	80.0
Stearyl Alcohol	25.0	500.0
Total	120.0	2400.0

Process:

1. Blend milled Stearyl Alcohol, Eudragit RLPO, Hydrocodone Bitartrate, and Eudragit RSPO using a Hobart Mixer.
2. Extrude the granulation using a Powder Feeder, Melt Extruder (equipped with the 6×1 mm die head), Conveyor, Lasermike, and Pelletizer.
   Powder feed rate—40 g/min; vacuum—~980 mBar
   Conveyor—such that diameter of extrudate is 1 mm
   Pelletizer—such that pellets are cut to 1 mm in length
3. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen.
4. Fill size 112 clear gelatin capsules with the pellets. Range: NLT (not less than) 114 mg and NMT (not more than) 126 mg.

One or more aversive agents as described herein can be incorporated into a capsule with the hydrocodone pellets, into the hydrocodone pellets, or on the hydrocodone pellets by one skilled in the art. The one or more aversive agents may be in releasable, non-releasable, or substantially non-releasable form or a combination thereof. Preferably, when pellets comprising the aversive agent(s) are incorporated into the capsule they are indistinguishable from the hydrocodone pellets.

EXAMPLE 15

Oxycodone HCl beads for capsule (Lot #814-40)

A sustained release oxycodone HCl bead formulation is prepared having the formula in Table 15 below.

TABLE 15

	Ingredients	Amt/unit* (mg)
Step 1. Drug layering	Oxycodone HCl	10.5
	Non-pareil beads (30/35 mesh)	45.349
	Opadry Clear	2.5

TABLE 15-continued

	Ingredients	Amt/unit* (mg)
Step 2. Sustained release coat	Eudragit RS30D (dry)	7.206
	Eudragit RL30D (dry)	0.379
	Triethyl citrate	1.517
	Cabosil	0.379
Step 3. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	1.899
	Cabosil	0.271
Total		70.0

Process:

1. Dissolve oxycodone HCl and Opadry (HPMC) in water. Spray the drug solution onto non-pareil beads in a fluid bed coater with Wurster insert.
2. Disperse Eudragit RS, Eudragit triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater.
3. Dissolve Opadry in water. Spray the solution onto the beads in the fluid bed coater.
4. Cure the beads at 60° C. for 24 hours.

One or more aversive agents as described herein can be incorporated into a capsule with the oxycodone beads, into the oxycodone beads, or on the oxycodone beads by one skilled in the art. The one or more aversive agents may be in releasable, non-releasable, or substantially non-releasable form or a combination thereof. Preferably, when beads comprising the aversive agent(s) are incorporated into the capsule they are indistinguishable from the oxycodone beads.

EXAMPLE 16

Controlled Release Hydromorphone

A sustained release hydromorphone HCl formulation is prepared having the formula in Table 16 below:

TABLE 16

Ingredients	Amt/Unit (mg)
Hydromorphone HCl	12.0
Eudragit RSPO	76.5
Ethocel	4.5
Stearic acid	27.0
Total	120.0

Process:

1. Blend milled Stearic acid, ethocel, Hydrocodone Bitartrate, and Eudragit RSPO using a V-blender.
2. Extrude the mixture using a Powder Feeder, Melt Extruder (equipped with the 6×1 mm die head), Conveyor, Lasermike, and Pelletizer.
   Powder feed rate—4.2 kg/hr; vacuum—~980 mBar
   Conveyor—such that diameter of extrudate is 1 mm
   Pelletizer—such that pellets are cut to 1 mm in length
3. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen.
4. Fill size #2 clear gelatin capsules with the pellets. Range: NLT 114 mg and NMT 126 mg.

One or more aversive agents as described herein can be incorporated into a capsule with the hydromorphone pellets, into the hydromorphone pellets, or on the hydromorphone pellets by one skilled in the art. The one or more aversive agents may be in releasable, non-releasable, or substantially non-releasable form or a combination thereof. Preferably, when pellets comprising the aversive agent(s) are incorporated into the capsule they are indistinguishable from the hydromorphone pellets.

EXAMPLE 17-20

Examples 9-12 can be repeated utilizing a sufficient amount of capsaicin in place of, or in addition to the aversive agents disclosed therein.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that obvious modifications can be made herein without departing from the spirit and scope of the invention. Such variations are contemplated to be within the scope of the appended claims.

What is claimed is:

1. A controlled release oral dosage form comprising:
from about 2.5 mg to about 320 mg oxycodone or a pharmaceutically acceptable salt thereof; and
a gelling agent comprising polyethylene oxide in an effective amount to impart a viscosity of at least about 10 cP when the dosage form is subjected to tampering by dissolution in from about 0.5 to about 10 ml of an aqueous liquid;
the dosage form providing a therapeutic effect for at least about 12 hours when orally administered to a human patient.

2. The controlled release oral dosage form of claim **1**, wherein the ratio of polyethylene oxide to oxycodone or pharmaceutically acceptable salt thereof is from about 1:40 to about 40:1.

3. The controlled release oral dosage form of claim **1**, wherein the ratio of polyethylene oxide to oxycodone or pharmaceutically acceptable salt thereof is from about 1:1 to about 30:1.

4. The controlled release oral dosage form of claim **1**, wherein the ratio of polyethylene oxide to oxycodone or pharmaceutically acceptable salt thereof is from about 2:1 to about 10:1.

5. The controlled release oral dosage form of claim **1**, wherein the aqueous liquid is water.

6. The controlled release oral dosage form of claim **1**, wherein the viscosity is imparted when the dosage form is subjected to tampering by dissolution in about 1 to about 3 ml of aqueous liquid.

7. The controlled release oral dosage form of claim **1**, wherein a viscosity of at least about 60 cP is imparted.

8. The controlled release oral dosage form of any one of claims **2**, **4**, **5**, **6** and **7**, wherein the polyethylene oxide possesses a weight-average molecular weight of from about 1,000,000 to about 10,000,000.

9. The controlled release oral dosage form of claim **8**, wherein the polyethylene oxide possesses a weight-average molecular weight of from about 1,000,000 to about 7,000,000.

10. The controlled release oral dosage form of claim **8**, wherein the polyethylene oxide possesses a weight-average molecular weight of about 5,000,000.

11. The controlled release oral dosage form of any one of claims **2**, **4**, **5**, **6** and **7**, wherein the oxycodone or pharmaceutically acceptable salt thereof comprises oxycodone hydrochloride.

12. The controlled release oral dosage form of claim **11**, comprising from about 10 mg to about 80 mg oxycodone hydrochloride.

13. The controlled release oral dosage form of claim **11**, comprising about 10 mg oxycodone hydrochloride.

14. The controlled release oral dosage form of claim **11**, comprising about 20 mg oxycodone hydrochloride.

15. The controlled release oral dosage form of claim **11**, comprising about 40 mg oxycodone hydrochloride.

16. The controlled release oral dosage form of claim **11**, comprising about 80 mg oxycodone hydrochloride.

17. The controlled release oral dosage form of claim **11**, wherein the polyethylene oxide:oxycodone hydrochloride ratio is from about 1:40 to about 40:1 by weight.

18. The controlled release oral dosage form of claim **11**, wherein the polyethylene oxide:oxycodone hydrochloride ratio is from about 1:1 to about 30:1 by weight.

19. The controlled release oral dosage form of claim **11**, wherein the polyethylene oxide:oxycodone hydrochloride ratio is from about 2:1 to about 10:1 by weight.

20. The controlled release oral dosage form of claim **11**, wherein the polyethylene oxide:oxycodone hydrochloride ratio is from about 1:15 to about 15:1 by weight.

21. The controlled release oral dosage form of claim **11**, wherein the polyethylene oxide:oxycodone hydrochloride ratio is from about 1:8 to about 8:1 by weight.

22. The controlled release oral dosage form of claim **11**, wherein the polyethylene oxide:oxycodone hydrochloride ratio is from about 1:3 to about 3:1 by weight.

23. The controlled release oral dosage form of any of claims **2**, **4**, **5**, **6** and **7**, wherein the viscosity is obtained when the dosage form is subjected to tampering by crushing and dissolution in the aqueous liquid.

24. The controlled release oral dosage form of any of claims **2**, **4**, **5**, **6** and **7**, wherein the viscosity is obtained when the dosage form is subjected to tampering by dissolution in the aqueous liquid with heating greater than 45° C.

* * * * *

CERTIFICATE OF SERVICE

I hereby certify that on August 12, 2015, I served a copy of the foregoing on all counsel of record by CM/ECF.

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 13,947 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Office 2007 in Times New Roman 14pt.

Dated: August 12, 2015

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